A Novel Methodology for the Asymmetric Synthesis of beta-Lactams and beta-Amino Acids

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Award date:
2012

Awarding institution:
University of Bath

A Novel Methodology for the Asymmetric Synthesis of β-Lactams and β-Amino Acids

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A thesis submitted for the degree of Doctor of Philosophy

University of Bath

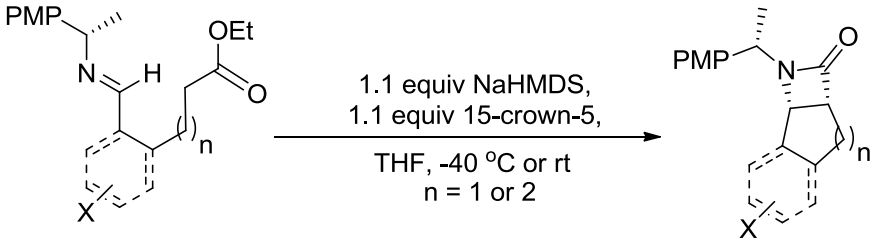
Department of Chemistry

May 2012

Signature …… **Date** ……

Abstract

The first example of an intramolecular ester enolate-imine cyclisation reaction for the asymmetric synthesis of polycyclic β-lactams and cyclic β-amino acid derivatives has been developed.



In Chapter 1, the synthesis of monocyclic β-lactams using intermolecular ester enolate-imine cyclisation reactions is reviewed. The use of chiral auxiliaries contained within the ester or imino functionality to control the diastereoselectivity of the reaction is discussed, as well as enantioselective approaches. The utilization of this methodology for the synthesis of natural products such as Taxol is described, as well as the use of polymer support protocols to improve the efficiency of this reaction.

In Chapter 2, the synthesis of an appropriate cyclisation substrate containing an ester and imino functionality with a chiral auxiliary fragment is reported. Appropriate conditions were established that enabled an intramolecular enolate-imine cyclisation reaction to be used for the synthesis of the tricyclic β-lactam benzocispentacin in good yield and excellent *de*. The formation of β-amino ester side products was investigated and an explanation for the production of β-lactams as major products over their corresponding β-amino esters is proposed. This protocol was then applied to the asymmetric synthesis of six benzocispentacin derivatives all with good yields and excellent *de*, with the configuration of one of these derivatives being confirmed by X-ray crystallography. A deprotection methodology was then established to afford their corresponding tricyclic NH-β-lactams and *cis* and *trans* bicyclic β-amino esters.

In Chapter 3, the newly devised methodology was also applied to acyclic substrates for the synthesis of the antifungal cispentacin. The ability to access both cis- and transpentacin in both high yields and excellent *de* as monomers for foldamer synthesis is reported. A small series of bicyclic β-lactam analogues was prepared in a short and efficient methodology, with the intramolecular enolate-imine cyclisation reaction being the key step to all these syntheses.

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Acknowledgements

Firstly, I would like to thank Dr Steven Bull for offering me the chance to do a PhD and for being both a supportive and encouraging supervisor. I would like to thank him for guiding me during my time at Bath and for an unforgettable experience. In addition, I am extremely appreciative to Steve, Jennifer Peed, Dr James Taylor and Dr Tracy Nixon for all of their support helping to proof read this thesis.

Thanks must also go to Dr James Muir at AstraZeneca who provided me with lots of support and chemicals throughout and also all the staff at Macclesfield who made my CASE placement a thoroughly enjoyable experience. I would like to thank Dr Andrew Leach for generously spending time to provide me with the computational modelling. In particular, I would also like to thank Dr Steve Coombes and Dr Tony Bristow who helped solve the structure of the particularly tricky cispentacin impurity, and also Dr Peter Moore who not only gave me lots of direction but was a good friend during my time at AZ.

During my time at Bath I have had the pleasure to work with many great people who have helped improve me as a chemist and made my PhD an experience I will never forget. During my first few years Dr Tracy Nixon, Dr Iwan Davies, Paul Fordred and Dr Hannah Maytum provided invaluable advice and support that helped me through my biggest educational learning curve. Thanks goes to all past and present members of the Bull group who have helped make my time so enjoyable and for putting up with me, in particular Robert Archer, Lucy Peacock, Richard Blackburn and Ruth Lawrence, all of whom have provided constant support and many entertaining moment. I would like to give special thanks to Jennifer Peed and Dr James Taylor for being really great friends when I needed them the most.

Finally, I would like to thank the people who have been there behind the scenes, who have constantly encouraged me and provided me with a sympathetic ear. Thanks to Dave Tickell and Denitza Williams who have always understood my PhD dilemmas and always given me great advice. I would like to thank my brother and sister, Samantha and Alex Evans, for always taking a keen interest in how it was all going. Most importantly I would like to thank my Mum and Dad who gave me the determination and ambition which enabled me to achieve this PhD.

Abbreviations

app.	Apparent
br.	Broad
Bu	Butyl
CAN	Ceric ammonium nitrate
COSY	Correlation spectroscopy
CSI	Chlorosulfonyl isocyanate
°C	Degrees Celsius
d	Doublet
δ	Chemical shift
DCM	Dichloromethane
DIPEA	*N*,*N*-Diisopropylethylamine
DMF	*N*,*N*-Dimethylformamide
DMI	1,3-Dimethyl-2-imidazolidinone
DMPU	*N*,*N*'-Dimethylpropyleneurea
DMSO	Dimethylsulfoxide
de	Diastereomeric excess
dr	Diastereomeric ratio
ee	Enantiomeric excess
Et	Ethyl
equiv.	Equivalent
g	Grams
HMBC	Heteronuclear Multiple Bond Correlation
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
hrs	Hours

Hz	Hertz
i	*iso*
J	Coupling Constant
LDA	Lithium diisopropylamide
LICA	Lithium isopropylcyclohexylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
m	Multiplet
m	*meta*
Me	Methyl
mcpba	*meta*-Chloroperoxybenzoic acid
mL	Millilitre
mol	Mole
NaHMDS	Sodium bis(trimethylsilyl)amide
NMR	Nuclear magnetic resonance
o	*ortho*
p	*para*
PCC	Pyridinium chlorochromate
Ph	Phenyl
PMP	*para*-Methoxyphenyl
PNB	*para*-Nitrobenzyl
ppm	Parts per million
PTSA	*para*-Toluenesulfonic acid
q	Quartet
rt	Room temperature
s	Singlet
t	*tert*

t	Triplet
TBAF	Tetrabutylammonium fluoride
TES	Triethylsilyl
Tf	Triflate
TMP	Trimethylolpropane
TMS	Trimethylsilyl
TMU	Tetramethylurea
THF	Tetrahydrofuran

1 The Ester Enolate-Imine Condensation Reaction for the Synthesis of β-lactams

1.1 Introduction

In the past century, the design and development of β-lactam antibiotics has been highly influential within drug discovery, due to their biological and pharmacological activity. The biological effects of the β-lactam ring system were first identified due to the discovery of penicillin in 1928, this led to the discovery of the most widely used of all the antimicrobial agents.[1] β-lactam antibiotics are highly successful therapeutic agents which can inhibit both penicillin binding proteins and serine proteases,[2] this is in addition to their bactericidal action on enzymes that cross-link the peptidoglycan of the bacterial cell wall. A variety of subgroups of β-lactam antibiotics have been developed and some of the most commonly synthesised targets include penicillins **1**, cephalosporins **2**, carbapenems **3** and the monocyclic norcardicins **4** (Figure 1). These antibiotics successfully interfere with the peptidoglycan cell wall synthesis, due to their ability to inhibit bacterial enzymes, transpeptidases and carboxypeptidases.[3]

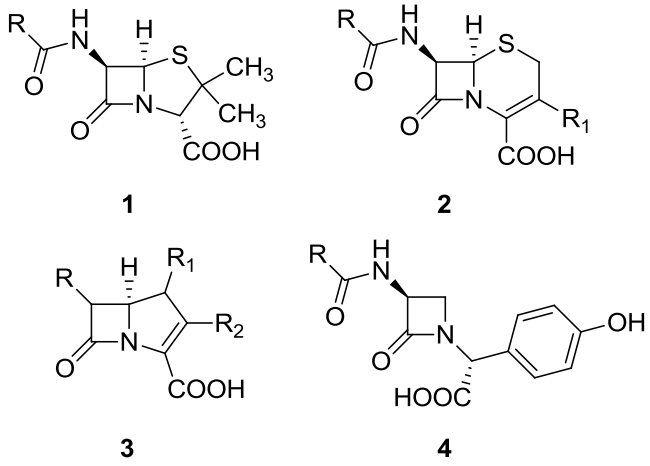
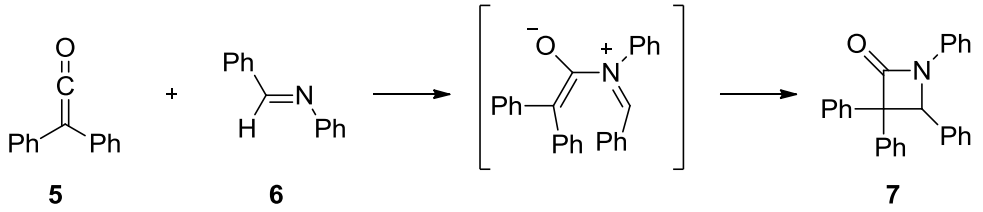


Figure 1- Examples of β-lactam antibiotic subgroups

In addition, β-lactam scaffolds have also been widely used as building blocks for synthesis of peptides, peptidomimetics, natural products and alkaloids, that have been subject to a series of detailed reviews.[4-5]

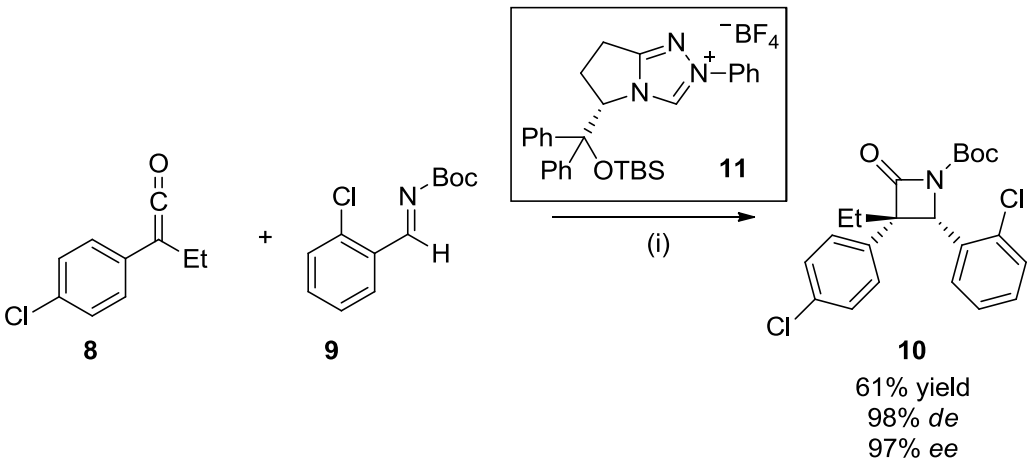
There are several main methods for the synthesis of β-lactams which include the Staudinger reaction, the Gilman-Speeter reaction and the Kinugasa reaction. In order to prepare β-lactams in their enantiopure form using these methodologies then either a chiral catalyst, chiral auxiliary or chiral starting materials need to be employed for stereocontrol.

The Staudinger [2+2] cycloaddition was first reported in 1907, which involved the cycloaddition of stable ketenes such as diphenylketene **5** with an imine **6** to furnish the first example of the strained four membered lactam ring **7**. [6] The nucleophilic addition of the nitrogen lone pair of the imine onto the carbon of the ketene results in the formation of a zwitterion which subsequently undergoes a cycloaddition forming a β-lactam (Scheme 1).



Scheme 1- Staudinger reaction producing first β-lactam[6]

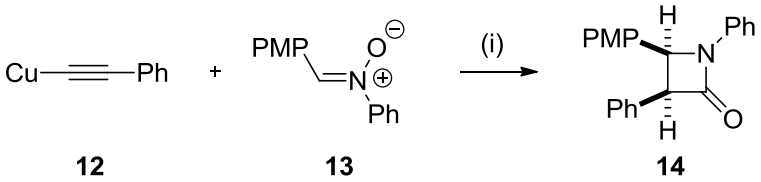
The Staudinger reaction is the most common methodology for the synthesis of β–lactams with much recent research aimed at developing an enantioselective reaction using chiral catalysts (Scheme 2).[7-8]



*Reagents & Conditions: (i) Catalyst **11** (10 mol%), Cs_2CO_3 (10 mol%), THF, rt*

Scheme 2- Chiral *N*-heterocyclic carbene catalysed Staudinger reaction[7]

In 1972, the synthesis of β-lactams was shown to be possible by reacting copper(I) phenylacetylide **12** with nitrones in anhydrous pyridine (Scheme 3). The reaction times were typically short, with readily available starting materials forming exclusively *cis*-β-lactams in good yield.[9]

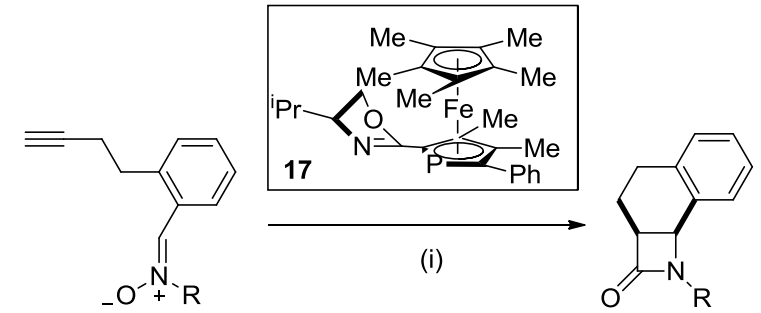


12 **13** **14**

Reagents & Conditions: (i) Pyridine, rt, 1hr

Scheme 3- First reported Kinugasa reaction[9]

Since its initial discovery, the scope and limitations of the Kinugasa reaction has been explored, with more recent examples obtaining β-lactams enantioselectively as well as the development of an intramolecular version of the reaction (Scheme 4).[10]



15
(R = *p*-carboethoxyphenol)

16
74% yield
88% *ee*

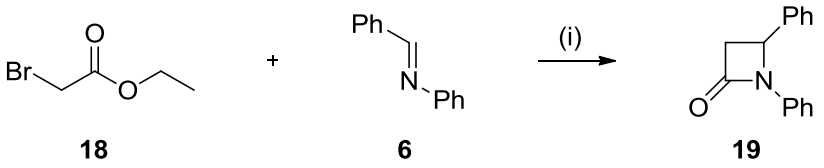
*Reagents & Conditions: (i) CuBr (5 %), ligand **17** (5 %), $CyNMe_2$, MeCN, 0 °C*

Scheme 4- Catalytic enantioselective intramolecular Kinugasa reaction[11]

Finally, the enolate-imine cyclisation reaction (Gilman-Speeter) is another highly utilized methodology employed for the synthesis of β-lactams. This methodology forms the basis of the research programme described in this thesis, and as a consequence the highlights of this important reaction will now be reviewed in detail.

1.2 Enolate-Imine Condensation Reactions - Introduction

The first enolate-imine condensation reaction was originally reported by Gilman and Speeter in 1943 who employed a Reformatsky type reaction of the zinc enolate of α-bromo-ester **18** with an imine for the production of an *N*-aryl-β-lactam such as **19** (Scheme 5).[12]

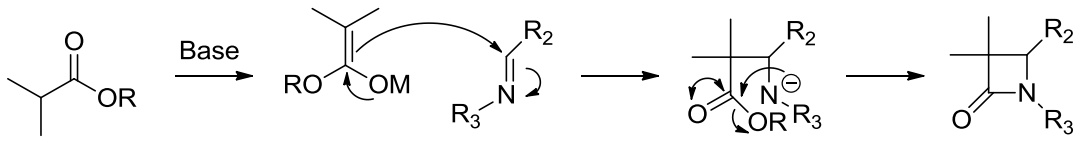


18 **6** **19**

Reagents & Conditions: (i) Zn, toluene

Scheme 5- First reported example of the Gilman-Speeter reaction for the synthesis of a β-lactam[12]

The ester enolate-imine condensation reaction can be considered analogous to the aldol condensation, whereby a metal enolate is generated that then effects nucleophilic attack at an imine to afford an intermediate β-amino ester, which subsequently undergoes a ring closure reaction to form a β-lactam structure (Scheme 6). This type of enolate-imine condensation reaction has attracted a large amount of interest, with much research concentrating on selectively accessing either *cis*- or *trans*-β-lactams. In this respect it represents an alternative to the established Staudinger methodology that involves [2+2] cycloaddition of a ketene and an imine.[6]



Scheme 6- Basic mechanism of the ester enolate-imine condensation reaction

Theoretical calculations support the proposed stepwise mechanism of the enolate-imine condensation reaction which were carried out to include the electrostatic effects of the solvent.[13] The reaction commences with C-C bond formation between the enolate and the imine which was calculated to be both irreversible and the rate determining step,[13] this is then followed by a rapid ring closure reaction that results in elimination of methoxide to afford the β-lactam ring.[13] The *cis*/*trans* stereochemistry of

the resulting β-lactam is dependent on the type of transition state formed in the initial nucleophilic addition step, which can proceed either *via* a chair or boat conformation depending on the conditions and type of metal counterion used for enolate formation (Figure 2).[14-16]

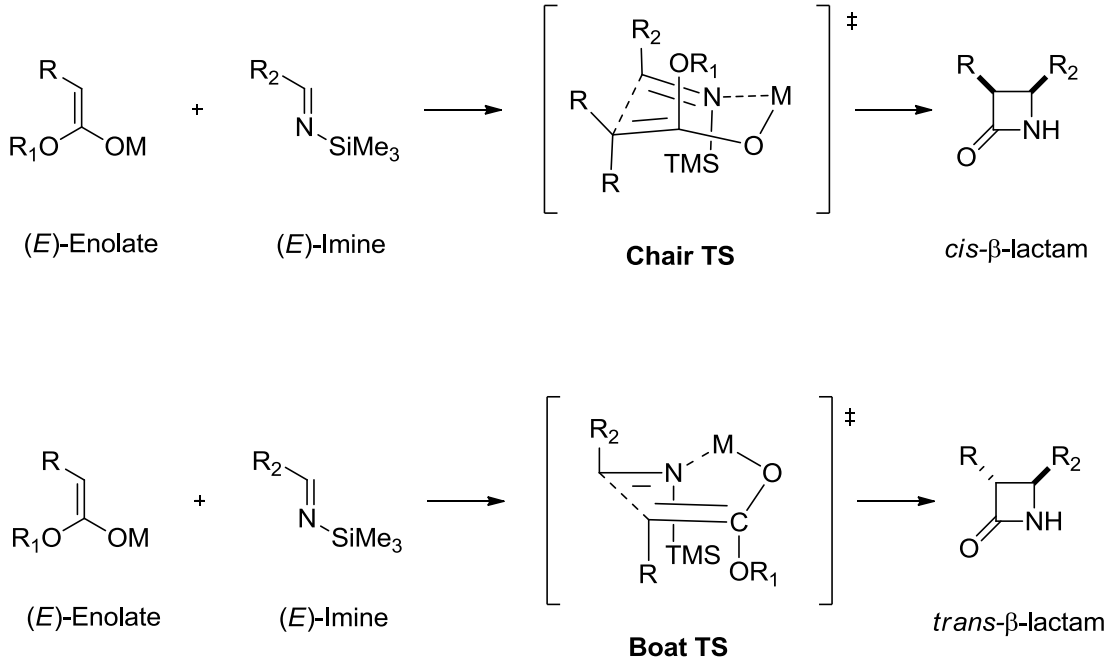


Figure 2- Effect of metal counterion on β-lactam formation

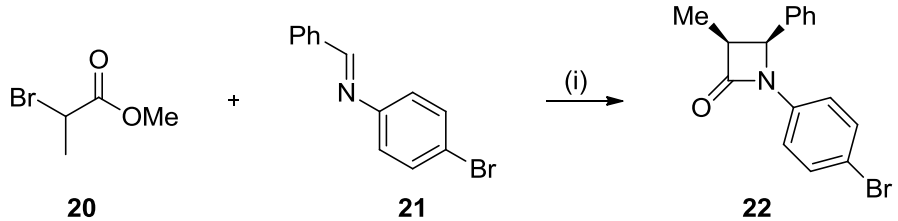
In 1989, the then emerging area of using enolate-imine cyclisation reactions for the synthesis of β-lactams was comprehensively reviewed, with a particular focus on the scope and limitation of different metal enolates on the yield and stereoselectivity of this reaction.[17] This review will now describe on progress in this area for the asymmetric synthesis of β-lactams, and demonstrate how this efficient methodology has been used for the synthesis of a number of medicinally useful β-lactam targets. For consistency and clarity, the review will follow the format originally used by Hart in 1989, first describing progress in generating and using different types of enolate species, followed by asymmetric development and natural product syntheses.[17] In this respect, it will briefly highlight the important factors known prior to 1989, and report important new developments that have contributed to this methodology now being widely used for the stereoselective synthesis of β-lactams.

1.3 Selected Metal Enolates

The greatest area of progress in demonstrating the potential of using enolate-imine cyclisation reactions for β-lactam formation has been in the use of lithium and/or zinc enolates, whilst protocols employing titanium, aluminium and boron enolates have all been used to selectively generate β-lactams with good levels of stereocontrol.

1.3.1 Zinc Enolates

The initial Reformatsky reaction carried out by Gilman *et al*. (Scheme 5) was further investigated, with a series of studies reporting that the reaction of zinc enolates of ethyl α-bromoacetate **20** with numerous *N*-aryl aldimines gave good yields of *N*-aryl-β-lactams (Scheme 7),[18] in particular the yields of 3-unsubstituted β-lactams were shown to be improved in the presence of ultrasound.[19] Investigations into the stereoselectivity of β-lactam formation revealed that the *cis*-β-lactam was normally formed as the major product when the α-substituent of the ester enolate was an alkyl group, or THF was used as solvent for the reaction.[20-21] Theoretical calculations revealed that reaction of the zinc enolate and imine occur *via* a twisted boat transition state in the case of tri- and tetra-coordinated zinc atoms in order to minimise steric interactions and electronic repulsion of electronegative atoms in the transition state.[22]

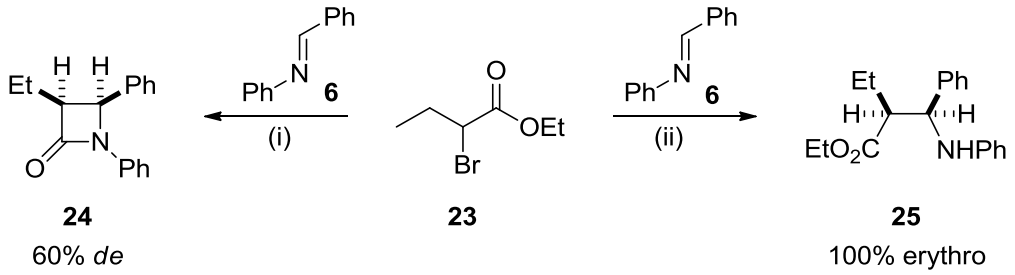


Reagents & Conditions: (i) Zn, THF, reflux

Scheme 7-Reaction of the zinc enolate of α-bromo-ester 20 with an aldimine for *cis*-β-lactam 22 synthesis[20]

It was also shown that varying the temperature of the reaction enabled either β-lactam **24**, or β-amino ester **25** to be accessed from these types of reactions (Scheme 8). It was proven that isomerization was taking place as only the *erythro*-isomer of the β-amino ester **25** was observed at lower temperature, whereas when the reaction was warmed to 42°C the *cis*-β-lactam **24** was isolated in 80% *de*, which suggests that the

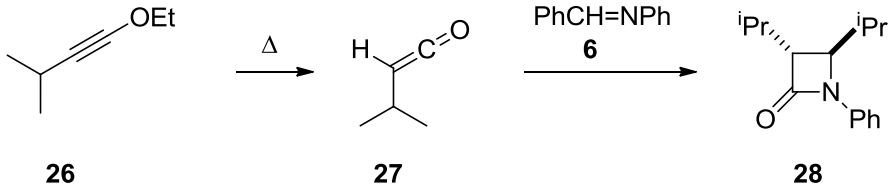
first step of the enolate-imine reaction might be a reversible reaction under these conditions.[23,24]



Reagents & Conditions: (i) Methylal, 42℃; (ii) Methylal, -10℃

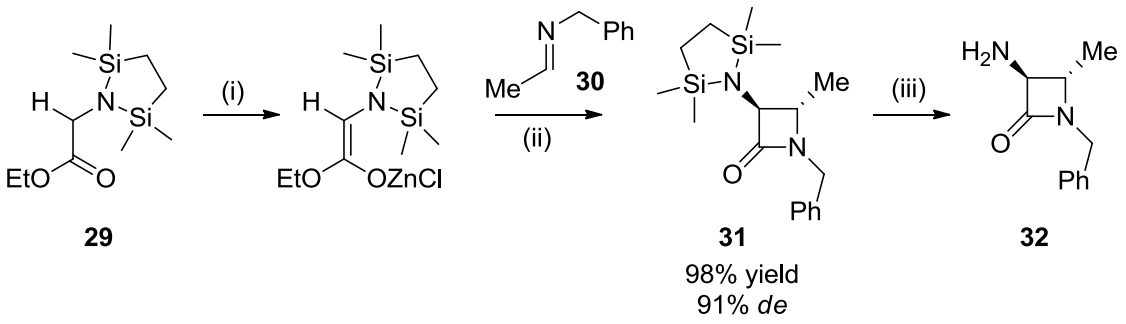
Scheme 8- Effects of reaction conditions on Reformatsky enolate-imine cyclisation products

Any suggestion that these cyclisation reactions were occurring *via* a ketene Staudinger-type mechanism were quickly ruled out, when it was shown that reaction of imine **6** with isopropyl-ketene **27** gave exclusively the corresponding *trans*-β-lactam **28** (Scheme 9).[25]



Scheme 9- Staudinger reaction resulting in synthesis of *trans*-β-lactam 28[25]

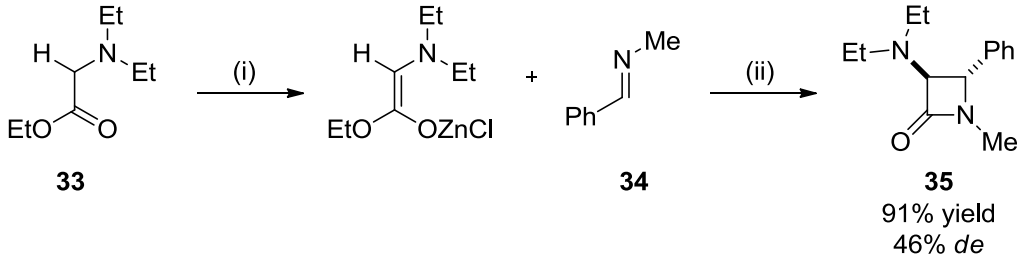
In 1991, the zinc enolate of *N*,*N*-disubstituted glycine ester **29** was generated *via* transmetallation of the lithium enolate, for the one-pot synthesis of *trans*-3-amino-2-azetidinones **31** in high yields and *de* (Scheme 10).[26] After an extensive study into the effects of the metal cation, solvent and substituents on the α-amino zinc ester enolates, it was found that the best *trans*- selectivity was obtained using apolar solvents and a bulky/electron withdrawing protecting group on the α-amino nitrogen of the enolate fragment.[26]



Reagents & Conditions: (i) a) LDA, Et_2O, -78°C b) $ZnCl_2$; (ii) -78°C to rt, H_2O; (iii)H^+/H_2O

Scheme 10- Synthesis of *trans*-2 azetinones using *N,N*-disubstituted glycine esters[26]

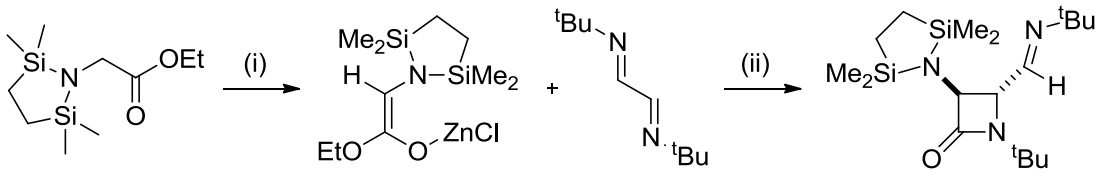
In addition, zinc enolates have previously been shown to interact with both activated (*N*-substituted with an electron withdrawing group) and unactivated imines (*N*-substituted with an electron donating group), which is advantageous when compared to lithium enolates which generally only react with activated imines. The catalytic use of $ZnCl_2$ was shown to marginally increase the *cis*:*trans* diastereoselectivity from 58:42 to 73:27 for β-lactam **35** (Scheme 11).[26]



Reagents & Conditions: (i) a) LDA b) 0.25 equiv. $ZnCl_2$; (ii) THF, reflux, 1hr

Scheme 11- Reformatsky reaction using *N*-alkyl-imines[26]

Functionalisation of C4 on the 3-amino-2-azetidinone has further effects on the *cis*:*trans* selectivity of the cyclisation reaction used for its formation. The bis-imine **36** had a much higher selectivity for the *trans* β-lactam compared to oxygen or sulfur analogues as it is proposed that these types of imines cyclise *via* a more restricted transition state (Scheme 12).[27]

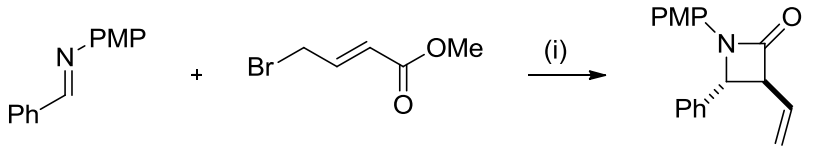


29 **36** **37**
92% yield
99% *de*

Reagents & Conditions: (i) a) LDA, Et_2O -78°C; b) $ZnCl_2$; (ii) -78°C to rt, H_2O

Scheme 12- C4 substituted *trans*-β-lactams[27]

More recently in 2003, it was found that treatment of 4-bromo-crotonate with a mixture of Zn/Cp_2TiCl_2 afforded a zinc enolate that reacted with imine **38** to exclusively afford a *trans*-β-lactam **40** in 81% yield (Scheme 13).[28]



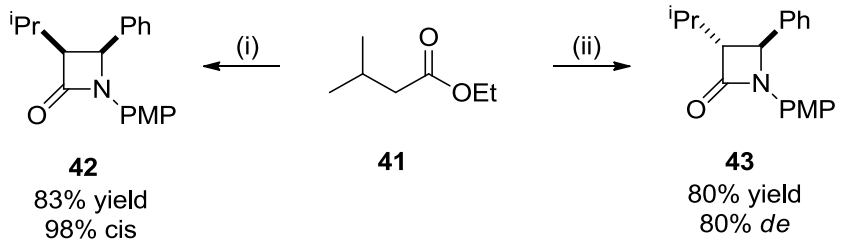
38 **39** **40**
81% yield
99% *de*

Reagents & Conditions: (i) Zn/Cp_2TiCl_2, THF, rt

Scheme 13- Zn/Cp_2TiCl_2 catalysed Reformatsky reaction[28]

1.3.2 Lithium Enolates

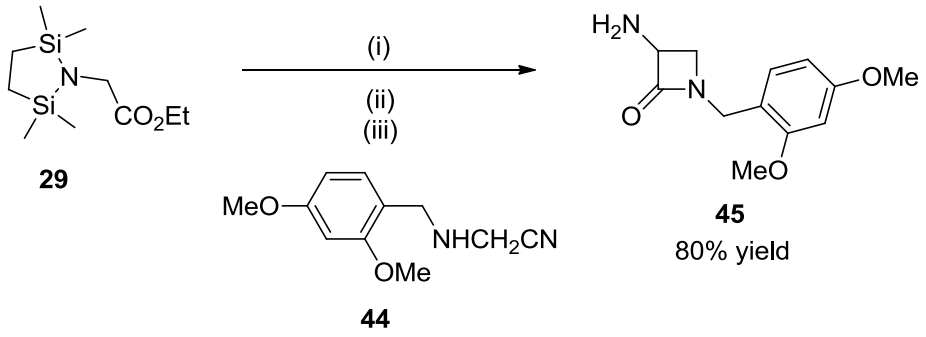
The first report of using lithium enolates for the enolate-imine condensation reaction was described in 1980, with lithium enolates of α,α-disubstituted acetates reacting with *N*-arylaldimines to furnish either *cis*- or *trans*-β-lactams in good yields and excellent *de*.[29] The conditions of the reaction, in particular the solvent, were shown to have a significant impact on the stereoselectivity of these reactions (Scheme 14). When THF was chosen as solvent then reaction of an (*E*)-enolate with an *N*-aryl-imine **38** resulted in formation of *cis*-β-lactam **42** as the major isomer in 83% yield, similar to the results observed using zinc enolates (Scheme 8). Conversely, when HMPA was added to the reaction, it resulted in a (*Z*)-enolate that selectively afforded a *trans*-β-lactam **43** in 80% yield as the major isomer.[29,30]



*Reagents & Conditions: (i) a) LDA, THF; b) N-benzylidene-4-methoxyaniline **38**, 25°C; (ii) a) LDA, THF; b) THF-HMPA, N-benzylidene-4-methoxyaniline **38**, 25°C*

Scheme 14- Effect of solvent on the β-lactam using lithium enolates[29]

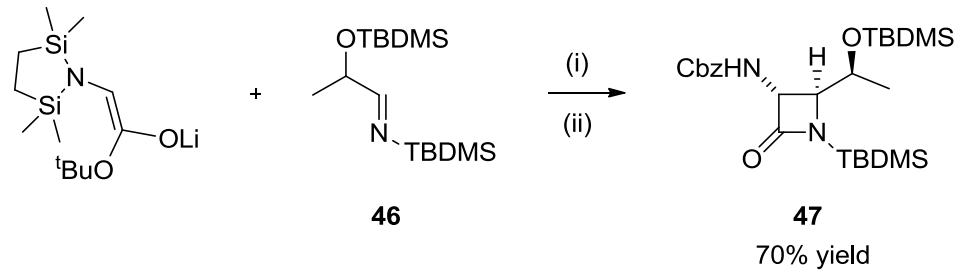
In 1985, Overman *et al.* demonstrated that *N*-substituted-α-amino nitriles **44** could be used as precursors to generate *N*-substituted formaldimines *in situ*, which then reacted with lithium enolates of *N*-protected glycine ester derivative **29** to afford the C_4-unsubstituted β-lactam **45** in high yield (Scheme 15).[31]



*Reagents & Conditions: (i) LDA (2.0 equiv.), THF (ii) Amine **44**; (iii) H_2O*

Scheme 15- Reaction of a lithium enolate to afford a 3-amino-β-lactam[31]

The development of a new methodology to generate *N*-(TIPS)- and *N*-(TBDMS)-imines enabled their effect on the selectivity of enolate-imine cyclisation reactions to be determined. The reaction of the lithium enolate of STABASE **29** and the *N*-(TBDMS)imine **46** was shown to exclusively afford the *trans*-β-lactam **47** in 70% yield (Scheme 16).[32] In comparison, *N*-(TMS)-imines are reported to selectively produce *cis*-β-lactams when used under the same conditions.



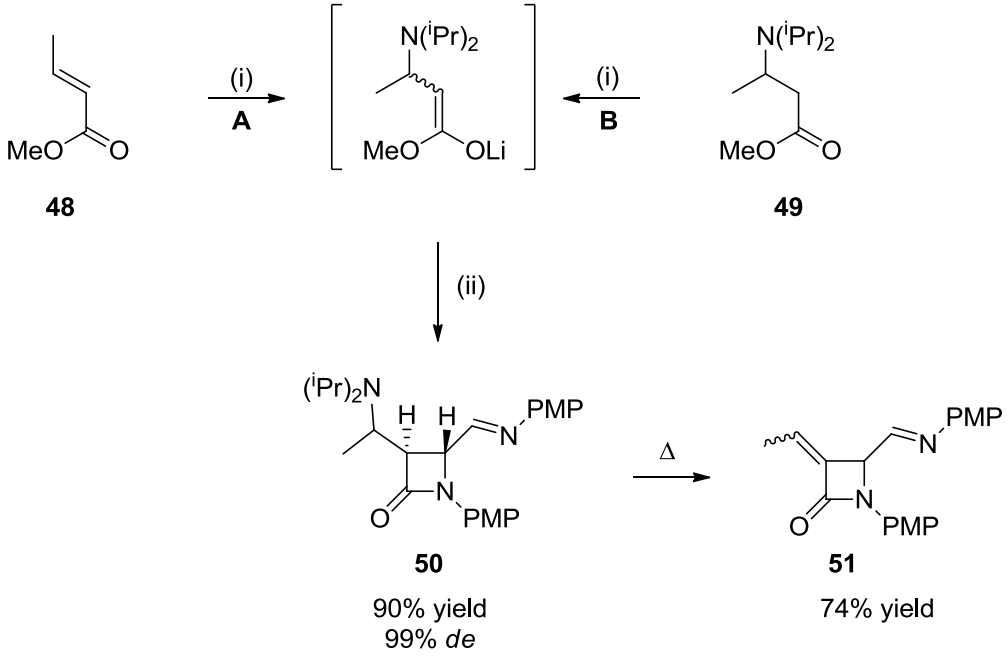
46 **47**

70% yield

Reagents & Conditions: (i) THF, -78°C; (ii) Na_2CO_3, CbzCl, acetone

Scheme 16- Use of *N*-(TBDMS)imines for β-lactam synthesis[32]

In addition, it has been demonstrated that the methodology for the synthesis of enolates can have significant implications on the stereochemistry of the resulting β-lactam **50**. For example, the enolate could be formed by either the conjugate addition of LDA to methyl crotonate **48** (**method A**), or *via* treatment of the corresponding β-amino ester **49** with LDA (**method B**). As such, the enolate was reacted with imine **52** to afford *trans*-β-lactam **50**, that was subsequently de-aminated to afford α-alkylidene-β-lactam **51** as a mixture of *E*/*Z* isomers, that were then screened as potential β-lactamase inhibitors (Scheme 17).[33]



48 **49** **50** **51**

90% yield
99% *de*

74% yield

*Reagents & Conditions: (i) LDA, -78°C, (ii) (ethane-1,2-diylidene)bis(4-methoxyaniline) **52***

Scheme 17- Synthesis of α-alkylidene-β-lactams[33]

Further work suggested that the stereoselectivity of the reaction is affected by the methodology used to generate the enolate for β-lactam synthesis. Method **A** produced β-lactam **50a** as the major diastereomer, whereas method **B** produced β-lactam **50b** as the major diastereomer.[34]

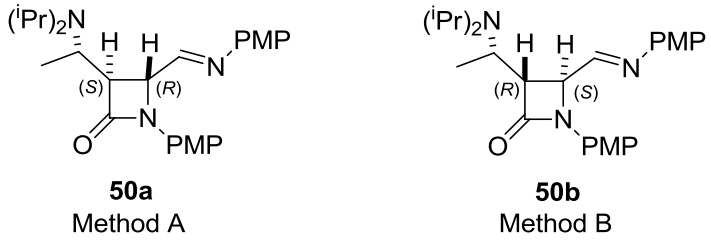
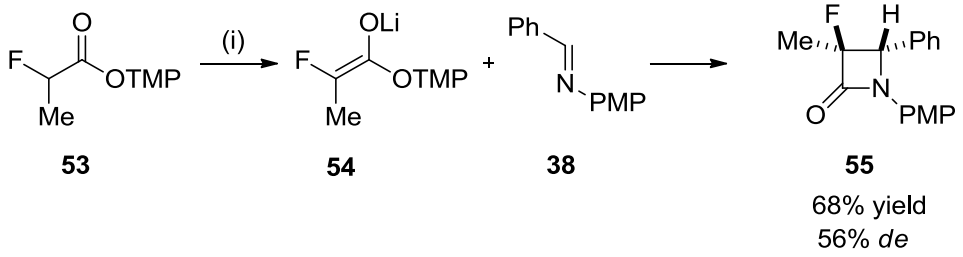


Figure 3- Major enantiomers formed during synthesis of β-lactam 50[34]

This methodology was then applied for the synthesis of α-ethylidene β-lactams using the enolate-imine reaction to allow access to polyoximic acids, these were subsequently used for the formation of a range of polyoxins.[34]

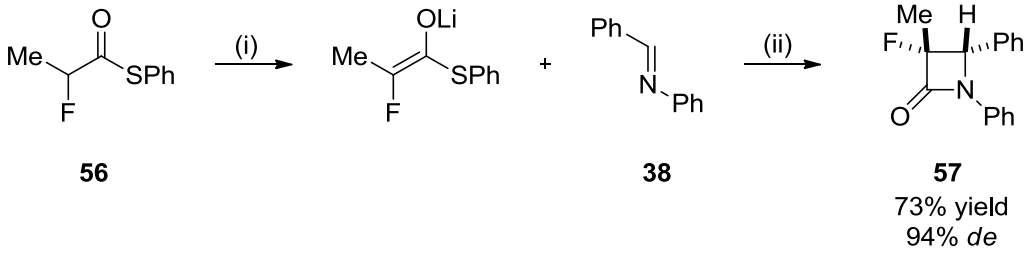
The result of α-hetero ester enolates with *N*-aryl imines has been well documented with the majority of substituents forming the *trans*-β-lactam.[14] An investigation into the stereoselective synthesis of 3-fluoro-azetidinones revealed that the use of the ketene-imine methodology to generate α-fluoro-β-lactams was much more selective than the corresponding ester enolate-imine condensation reaction. A series of experimental conditions were investigated which revealed that the best conditions for the reaction of lithium fluoro-enolate **54** with *N*-aryl-imine **38** resulted in the predominant formation of the *trans*-β-lactam **55** in 56% *de* and 68% yield (Scheme 18).[35]



Reagents & Conditions: (i) LDA, -78°C, THF

Scheme 18- Synthesis of 3-fluoro-azetidinones[35]

More recently, alternative conditions for the synthesis of these types of 3-fluoro azetindinones have been devised using the (*Z*)-enolate of thioester **56** which afforded the *cis*-β-lactam **57** in 73% yield and 94% *de* (Scheme 19).[36]

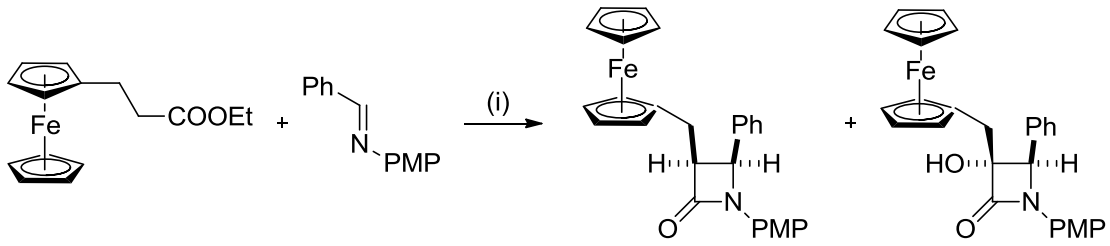


56 **38** **57**
73% yield
94% *de*

Reagents & Conditions: (i) LDA, -78°C, THF; (ii) rt, 4hrs

Scheme 19- Synthesis of 3-fluoro azetidinones using thioesters[37]

Previously, the highly selective synthesis of *cis*-β-amino acyl iron complexes has been reported using lithium enolates of chiral racemic iron acyl complexes and *N*-aryl imines.[38] In 2001, the preparation of β-lactams containing ferrocene units at the 3-position *via* reaction of the lithium enolate of ethyl 3-ferrocenylpropanoate with imine **38** was reported. This ester enolate-imine condensation produced β–lactam **59** as the major product and the hydroxy-β-lactam **60** as a minor side product (Scheme 20).[39]



58 **38** **59** **60**
40% yield
52% *de*
22% yield

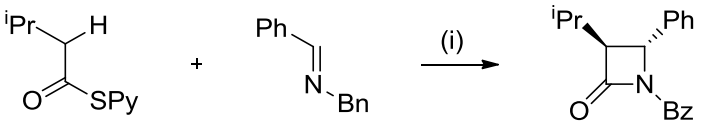
Reagents & Conditions: (i) LDA, -78°C, THF

Scheme 20- Synthesis of C3-ferrocene substituted β-lactams[39]

1.3.3 Titanium Enolates

Cinquini *et al.* originally reported on the synthesis of β-lactams *via* the reaction of titanium enolates of 2-pyridylthioesters with imines,[40] which revealed that an increase in

steric bulk on the α-substituent resulted in an increase in *trans* selectivity. For example, it was shown that reaction of the lithium enolate of thioester **61** containing an α-isopropyl group with *N*-benzyl-imine **62** gave *trans*-β-lactam **63** in an 83% yield (Scheme 21).



61 **62** **63**

83% yield
68% *de*

Reagents & Conditions: (i) $TiCl_4$, Et_3N, -78°C to 0 °C, 6hrs

Scheme 21-Reaction of the enolate of thioester 61 with imine 62 affords *trans*-β-lactam 63 with good levels of stereocontrol[40]

It was proposed that this *trans*-β-lactam **63** was formed *via* a transition state that involved an intramolecular chelate between the pyridine nitrogen atom and the titanium counterion of the enolate (Figure 4).[40]

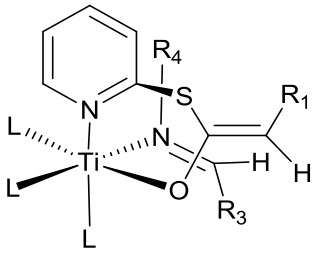
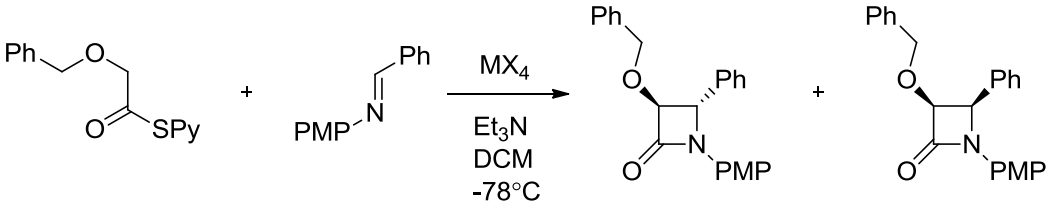


Figure 4- Transition state of titanium enolate of 2-pyridylthioester that affords β-lactam 63 with good levels of (*trans*)-β-lactam selectivity[40]

The reactivity of titanium (IV) and tin (IV) enolates of the thiopyridyl ester **64** with imines was investigated in order to determinine whether improved *trans*:*cis* ratios could be obtained.[41] Tin enolates were found to afford better levels of stereocontrol with the use of $SnCl_4$ affording the corresponding *cis*-β-lactam **66** in 80% de, whilst $SnBr_4$ gave *trans*-β-lactam **65** in 74% *de* (Table 1).[41]

Table 1- Comparison of the reactivity of tin(IV) and titanium (IV) enolates with *N*-aryl-imines[41]

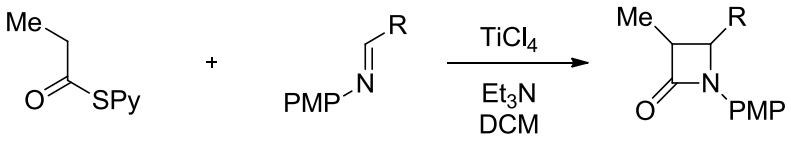


64 **38** **65** **66**

Entry	MX_4	Yield (%)	***trans*:*cis* ratio**
1	$TiCl_4$	74	39:61
2	$TiBr_4$	56	73:27
3	$SnCl_4$	18	10:90
4	$SnBr_4$	92	87:13

The influence of the imine structure on the *trans*/*cis* ratio of these cyclisation reactions was further investigated by analysing the diastereoselectivity for reactions of enolates of achiral thioesters with achiral imines containing different substituents. It was found that *trans*-β-lactams were formed as a result of reaction of imines with bulky and non-chelating heteroatoms, whereas *cis*–β-lactams were formed as major products from imines that contained small or chelating groups.[42]

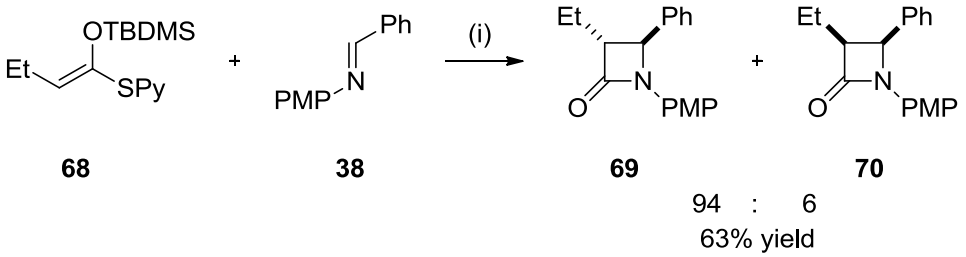
Table 2- Effect of imine substituent on *trans*/*cis* ratio[42]



67

Entry	R	Yield (%)	***trans*:*cis* ratio**
1	Ph	99	70:30
2	HC=CHPh	99	60:40
3	*n*-Pr	48	37:63
4	$CH_2OTBDPS$	40	46:54
5	CH_2OBn	40	23:77

Furthermore, in an attempt to determine how the enolate geometry of an achiral thioester affects the *trans*/*cis* ratio during β-lactam formation, enolate **68** was trapped as a silylketene acetal. The trapped (*E*)-enolate (geometry determined by ^{1}H NMR spectroscopy) was subsequently reacted with achiral imine **38** and a Lewis acid, titanium(IV)chloride, to afford the *trans*-β-lactam **69** in high *de*.[43] In general, when the titanium (*E*)-enolate of the silyl ketene thioacetal was formed, the *trans* β-lactam was observed in the corresponding (*E*)/(*Z*) ratio.[43]

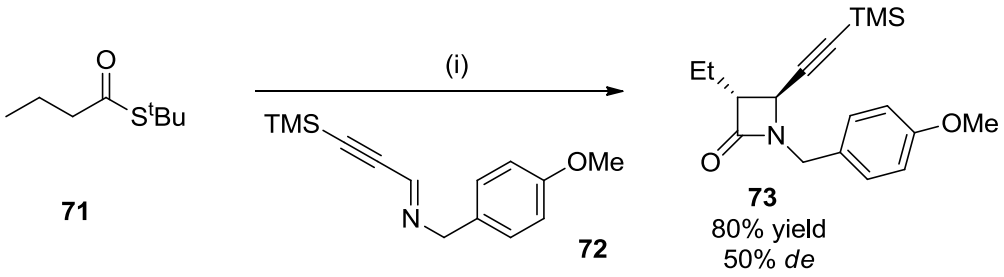


Reagents & Conditions: (i) $TiCl_4$, DCM, 0°C to rt, 12hrs

Scheme 22- Ketene-silyl acetals as nucleophiles for β-lactam synthesis[43]

1.3.4 Other Conditions

The reaction of aluminium enolates of thioesters **71** with *N*-alkylimines **72** for the synthesis of a range of analogues of *trans*-β-lactams **73** in high yield and good *de* was first reported in 1987 (Scheme 23).[44,45] Alternatively, if a more sterically demanding ester substituent is used, such as an isopropyl group, then the *cis*-β-lactam predominates.

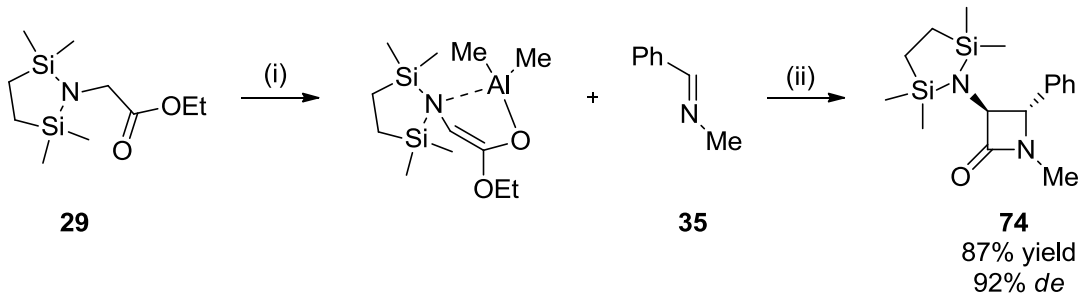


*Reagents & Conditions: (i) a) LDA, THF; b) Et_2AlCl; c) Imine **72***

Scheme 23- Aluminium enolate and enolisable *N*-alkylimines for β-lactam formation[45]

This use of aluminum enolates was further exploited *via* a transmetallation of the lithium enolate of *N*,*N*-disubsituted glycine thioester **29** with an excess of Me_2AlCl which gave

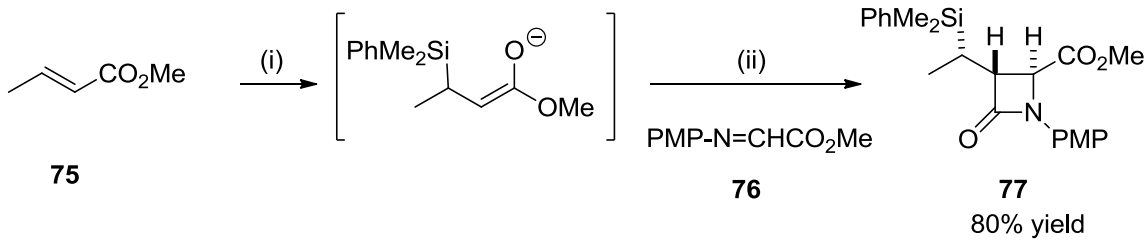
a dialkylaluminium (*Z*)-enolate that reacts with *N*-methyl-imine **35** to furnish *trans*-β-lactam **74** in 92% *de* and 87% yield (Scheme 24).[46]



Reagents & Conditions: (i) LDA, Me_2AlCl (1.2 equiv.), benzene, 0°C to rt, 0.5hrs; (ii) reflux

Scheme 24- Synthesis of aluminium enolates and effect on stereoselectivity of β-lactam[46]

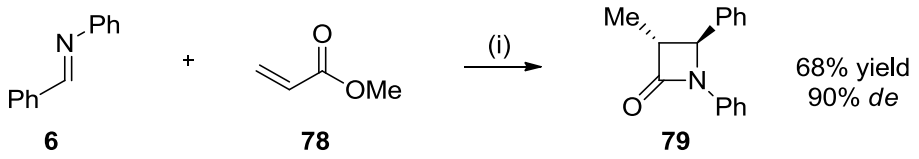
The ability to isolate a single diastereomer of a β-lactam in good yield using an organocopper ester enolate-imine condensation reaction was first reported during the synthesis of the antibiotic thienamycin.[47] Conjugate addition of a silyl anion generates an enolate from ester **75** that then reacts with imine **76** to afford *trans*-β-lactam **77** with good levels of stereocontrol.



*Reagents & Conditions: (i) $(PhMe_2Si)_2CuCNLi_2$, THF, 0 °C, 20 mins; (ii) Imine **76**, THF, 0 °C to rt, 3 hrs*

Scheme 25- Organocopper ester enolate-imine condensation reaction[47]

More recently, a novel strategy for the generation of iridium enolates was developed involving an *in situ* reduction of an α,β-unsaturated ester **78** with a iridium hydride species, that generates an iridium enolate *in situ* which reacts with *N*-aryl-imine **6**, to afford the *trans*-β-lactam **79** in 68% yield and 90% *de* (Scheme 26).[48]

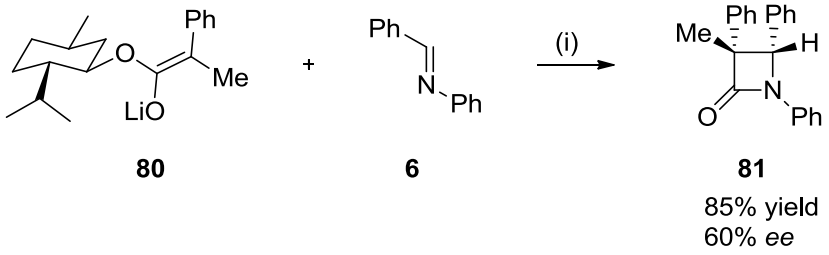


Reagents & Conditions: (i) 2.5mol% [(cod)IrCl]$_2$, 10mol% P(OPh)$_3$, Et$_2$MeSiH, 60°C, 6hrs

Scheme 26- Iridium catalysed reductive coupling of imines and acrylates[48]

1.4 Chiral Esters

The ability to prepare enantiopure β-lactams is of great importance as they can be used as both versatile chiral building blocks for synthesis or as important biologically active agents. The first significant report of carrying out ester enolate-imine cyclisation reactions using a chiral ester fragment was reported in 1980, where it was demonstrated that reaction of the lithium enolate of menthyl ester **80** with imine **6** gave β-lactam **81** in 60% *ee* (Scheme 27).[29] The use of a chiral ester fragment to direct stereocontrol in this manner has the advantage that the final β-lactam cyclisation step results in cleavage of the chiral alcohol fragment, and as such does not require an additional deprotection step.

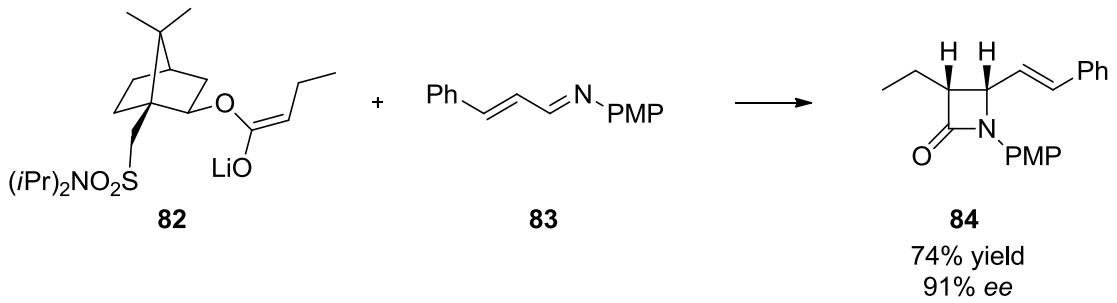


Reagents & Conditions: (i) LDA, THF

Scheme 27- Asymmetric synthesis of β-lactam synthesis using a menthyl ester for diastereocontrol[29]

Furthermore, several alternative chiral auxiliaries were trialed, with the most successful the (*E*)-lithium enolate of α-monosubstituted chiral ester **82**, which was reacted with

cinnamaldimine **83** to produce the major β-lactam **84** in 74% yield and an excellent 91% ee.[49]



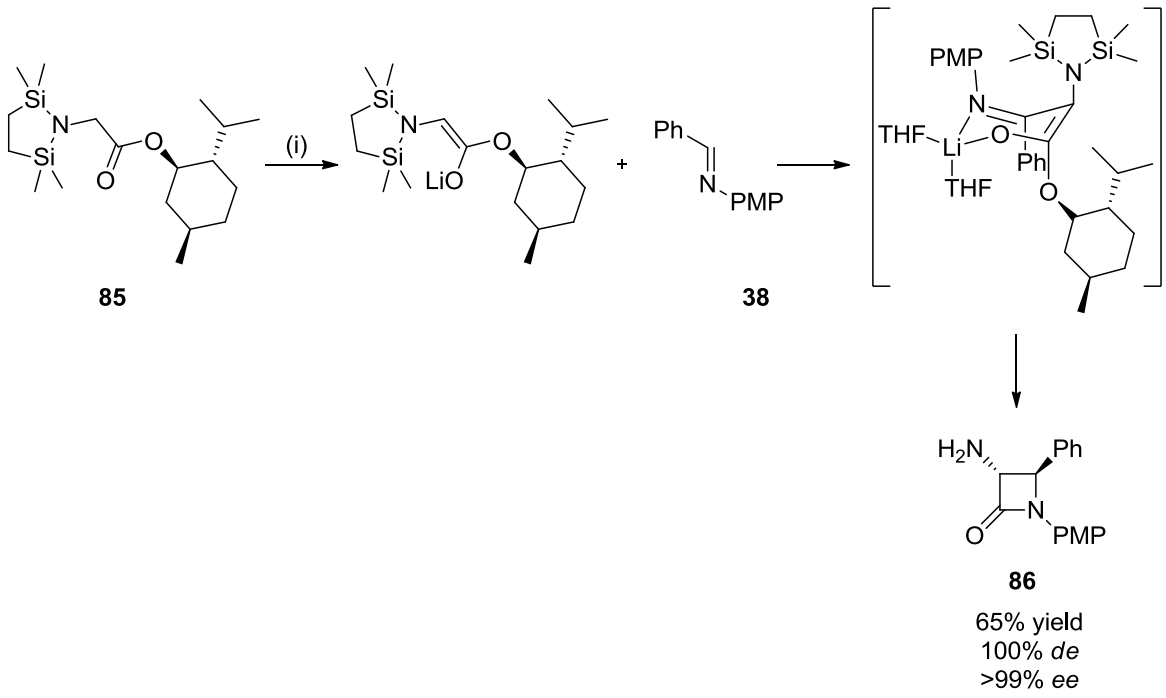
82 **83** **84**

74% yield
91% *ee*

Scheme 28- Synthesis of β-lactams using camphor derived esters[49]

Since these initial reports there have been several major developments in this area, with chiral esters being successfully employed for the synthesis of highly functionalized β-lactams with high levels of stereocontrol.

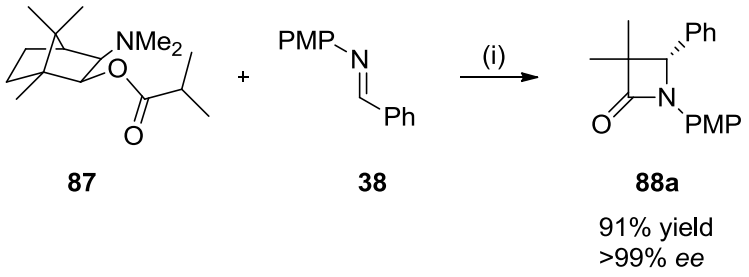
In 1990, Ojima *et al.* described the reaction of *N*,*N*-bis(silyl)glycinate chiral esters **85**, that contain a (-)-menthyl ester group, with *N*-aryl-imine **38** to afford *trans*-β-lactams with good levels of stereocontrol.[50] The stereochemistry of the initial cyclisation reaction was explained using a transition state, involving attack of a chiral (*Z*)-enolate at the *Re*-face of the imine, to afford after subsequent cyclisation the *trans*-(3*R*,4*R*)-β–lactam **86** in >99% *ee* (Scheme 29).[50] In addition, lithium enolates of chiral esters containing both (+)- and (-)-*trans*-2-phenyl-1-cyclohexyl fragments were also shown to be successful in affording β-lactam **86** in 58% yield and in >99% *ee.*



Reagents & Conditions: (i) LDA, THF, -78°C, 4hrs

Scheme 29- Chiral enolate ester-imine condensation using a (-)-menthyl derived chiral auxiliary[50]

When the *cis-exo* isomer of (+)-camphor was used as the chiral auxiliary, then the lithium enolate of ester **87** gave the substituted (*S*)-β-lactam **88a** in 91% yield and very high *ee* (Scheme 30).[51]

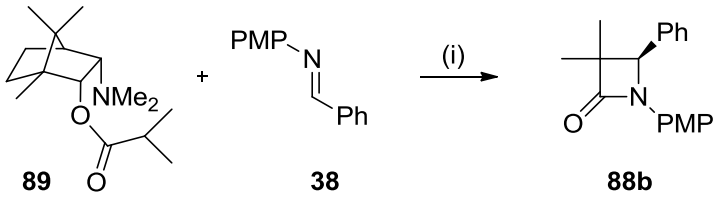


Reagents & Conditions: (i) LDA, Et_2O, -78°C to -40°C

Scheme 30- Ester enolate-imine condensation reaction controlled by a (+)-camphor auxiliary[51]

Alternatively, when the *cis-endo* isomer of (+)-camphor was used as the chiral auxiliary, then the opposite configuration was observed yielding an (*R*)-β-lactam **88b** in 92% *ee*,

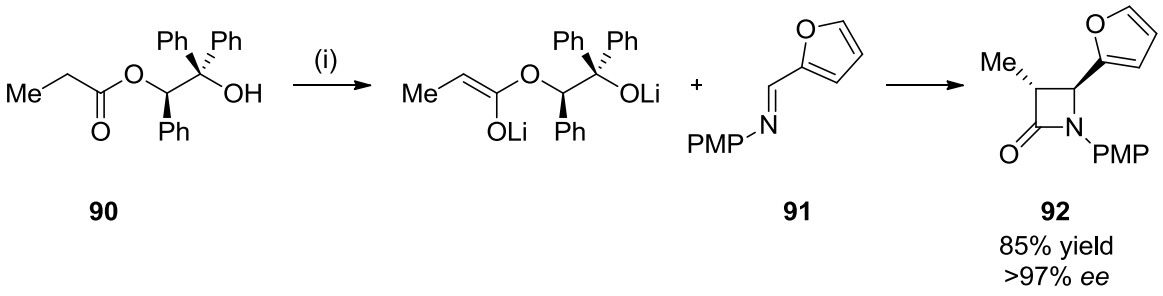
with the addition of stoichiometric amounts of additives such as triethylborane or tetrabutyltin being shown to further improve selectivity levels.[51]



Reagents & Conditions: (i) LDA, Et_2O, -78°C to -40°C

Scheme 31- Ester enolate-imine condensation reaction controlled by a (+)-camphor auxiliary[51]

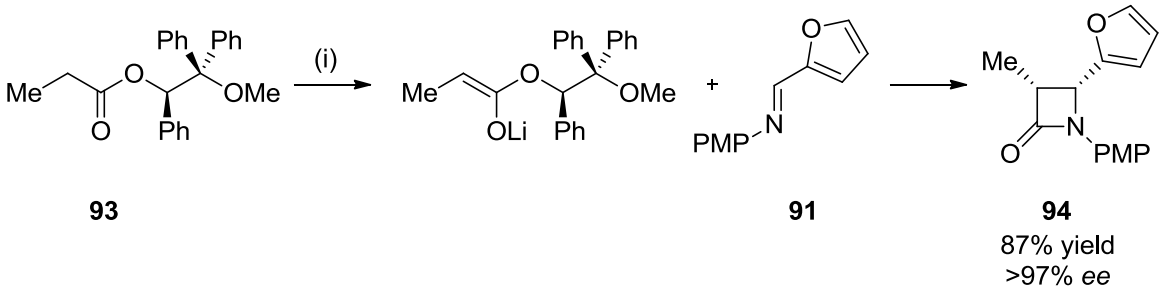
In 1995, it was reported that it was possible to exclusively access either *cis*- or *trans*-β-lactams in high *ee* using different triphenylglycol derived esters as the nucleophilic component. The (*R*)-ester **90** was doubly deprotonated to afford a chiral propionate enolate, that was reacted with imine **91** to afford the *trans*-β-lactam **92** in >97% *ee* (Scheme 32).[52]



Reagents & Conditions: (i) LDA (2.0equiv.), THF, -50°C to -35°C

Scheme 32- Double lithiated chiral propionate for *trans* β-lactam synthesis[52]

Conversely, when the *O*-methyl derivative of a (*R*)-triphenylglycol ester **93** was monodeprotonated to afford enolate then reaction with imine **91** gave the alternative *cis*-β-lactam **94** in >97% *ee* (Scheme 33).[52]

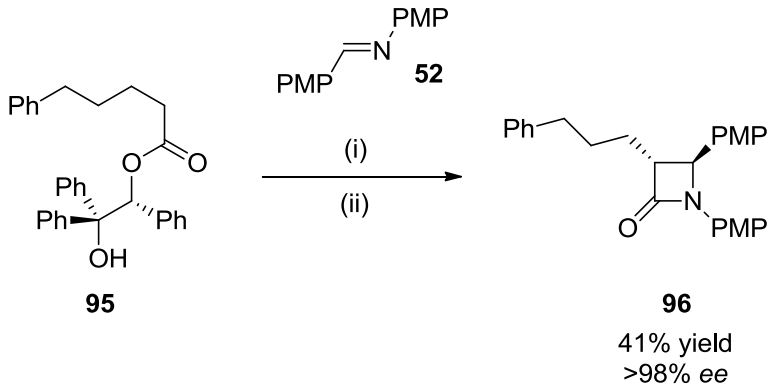


93 **91** **94**
87% yield
>97% *ee*

Reagents & Conditions: (i) LDA (1.0equiv.), THF, -50°C to -35°C

Scheme 33- Mono-lithiated chiral propionate for *cis* β-lactam synthesis[52]

This methodology was subsequently applied to the asymmetric synthesis of the cholesterol absorption inhibitor (-)-SCH 48461 **96**, which was successfully produced in >98% *ee* (Scheme 34).[53]

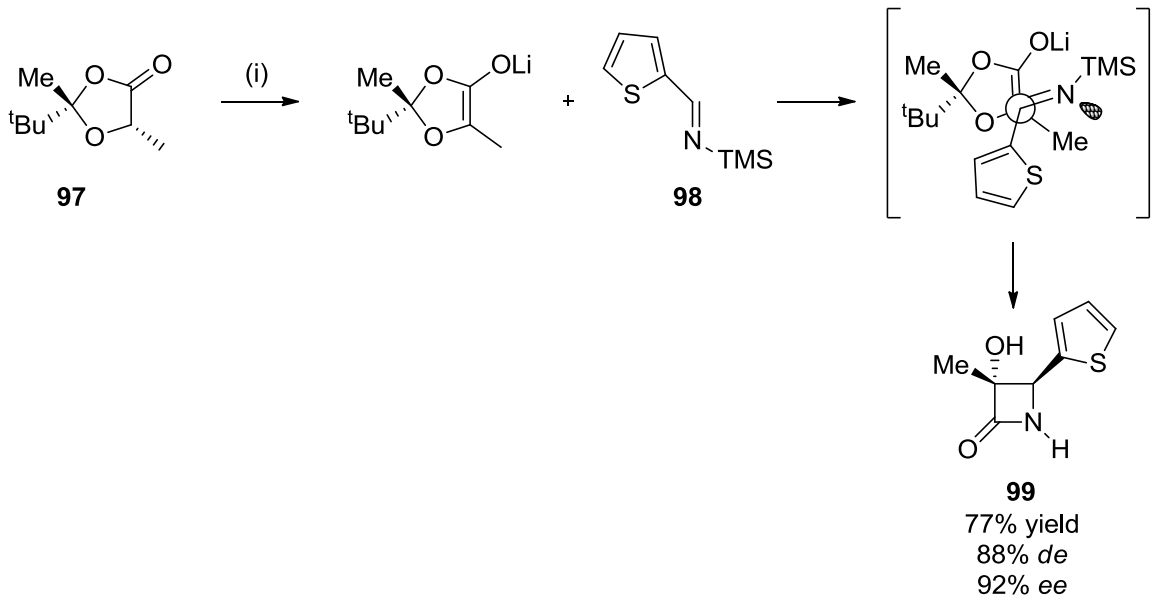


95 **96**
41% yield
>98% *ee*

*Reagents & Conditions: (i) LiN(i-Pr)$_2$ (2.0equiv.), THF, -78 °C to -65 °C, 1hr; (ii) Imine **52**, THF, -78 °C to rt*

Scheme 34- Synthesis of (-)-SCH 48461 using triphenylglycol ester 95 [53]

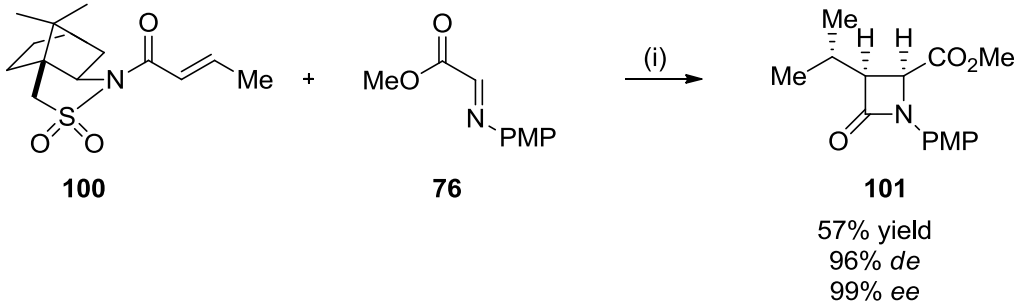
The highly enantioselective construction of chiral (3*R*)-3-alkyl-3-hydroxy-β-lactams was made possible by generating an (*E*)-enolate from Seebach's auxiliary **97**, which reacts with the imine **98** from its *Re* face- *trans* to the bulky ^{t}butyl group chiral auxiliary fragment. The resultant intermediate then cyclises onto its carbonyl group, with elimination of the chiral auxiliary fragment affording β-lactam **99** in 94% yield after recrystallisation (Scheme 35).[54]



Reagents & Conditions: (i) LHMDS, -78°C, THF/HMPA

Scheme 35- Enantioselective synthesis of β-lactams using 1,3-dioxolan-4-ones[54]

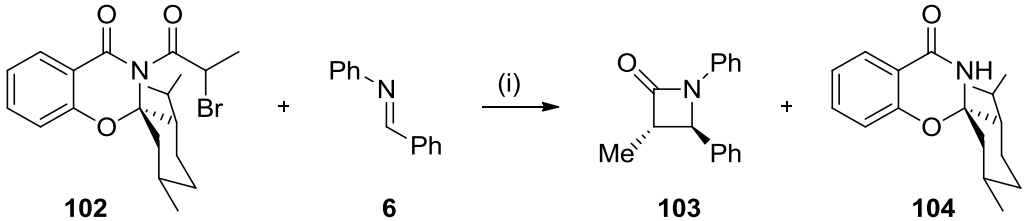
Several years after the use of an organocopper ester enolate-imine condensation reaction using an achiral imine and an achiral ester (Scheme 25), the full potential of organocuprate catalysed conjugate addition reactions was established for the asymmetric conjugate addition of carbon nucleophiles to chiral α,β-unsaturated esters **100**. The resultant enolate intermediate was reacted with a glyoxylate imine **76** to afford β-lactam **101** in good *de* and *ee* (Scheme 36).[55] This multi-component strategy was subsequently employed for the asymmetric synthesis of the antibiotic family Nikkomycins.[56]



Reagents & Conditions: (i) Me_2CuLi, 0°C, THF, 3hrs

Scheme 36- Use of lithium dialkylcuprates for the asymmetric synthesis of β-lactams[55]

More recently in 2004, an efficient and diastereoselective synthesis of *trans*-β-lactams was reported using enolates derived from a carboximide auxiliary prepared from salicylamide.[57] This classic Reformatsky reaction occured *via* generation of a zinc (*Z*)-enolate that was shown to afford either *trans*-β-lactam **103**, or β-amino amide derivatives, depending on the nature of the substrate substituents (Scheme 37).[57]



102 **6** **103** **104**

65% yield
99% *de*
85% *ee*

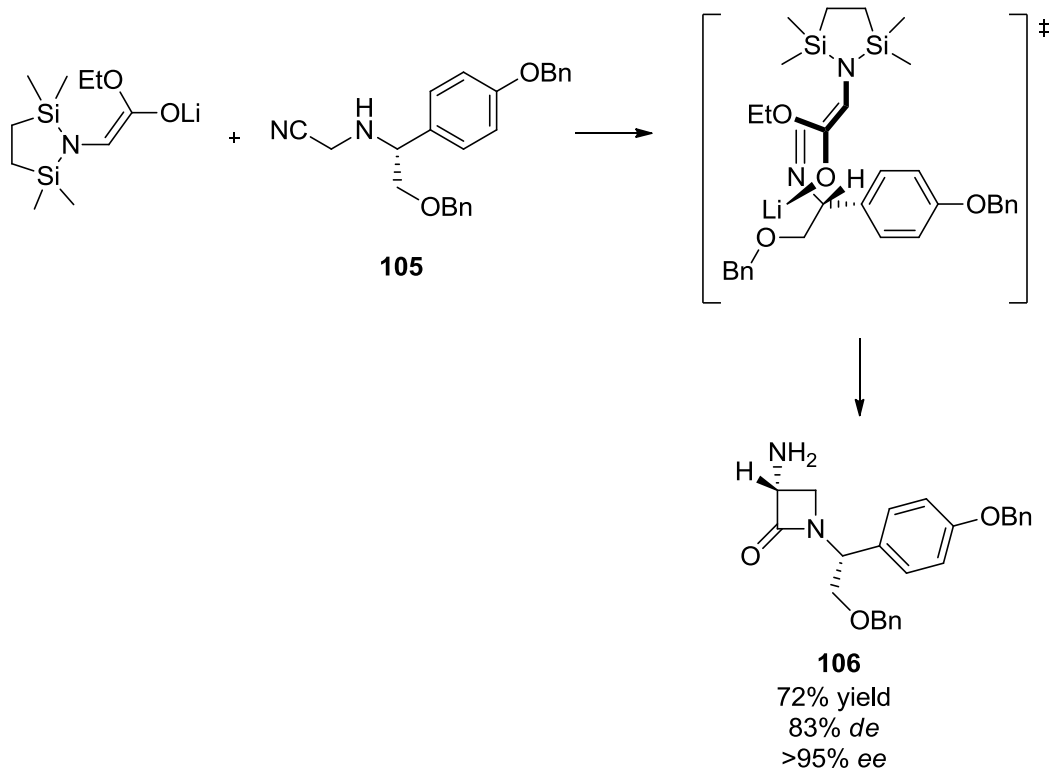
Reagents & Conditions: (i) Zn, THF, reflux, 2hrs

Scheme 37- Enantioselective Reformatsky reaction using a chiral auxiliary[58]

It was possible to rationalize the stereochemistry of the reaction by reasoning that the (*Z*)-enolate formed attacks on the *Re*-face due to steric hindrance from the isopropyl group blocking the *Si*-face. This results in the formation of the (3*R*,4*S*) β-lactam as the major isomer which was isolated in an 85% *ee,* whilst the chiral auxiliary could be recycled as required.

1.5 Chiral Imines

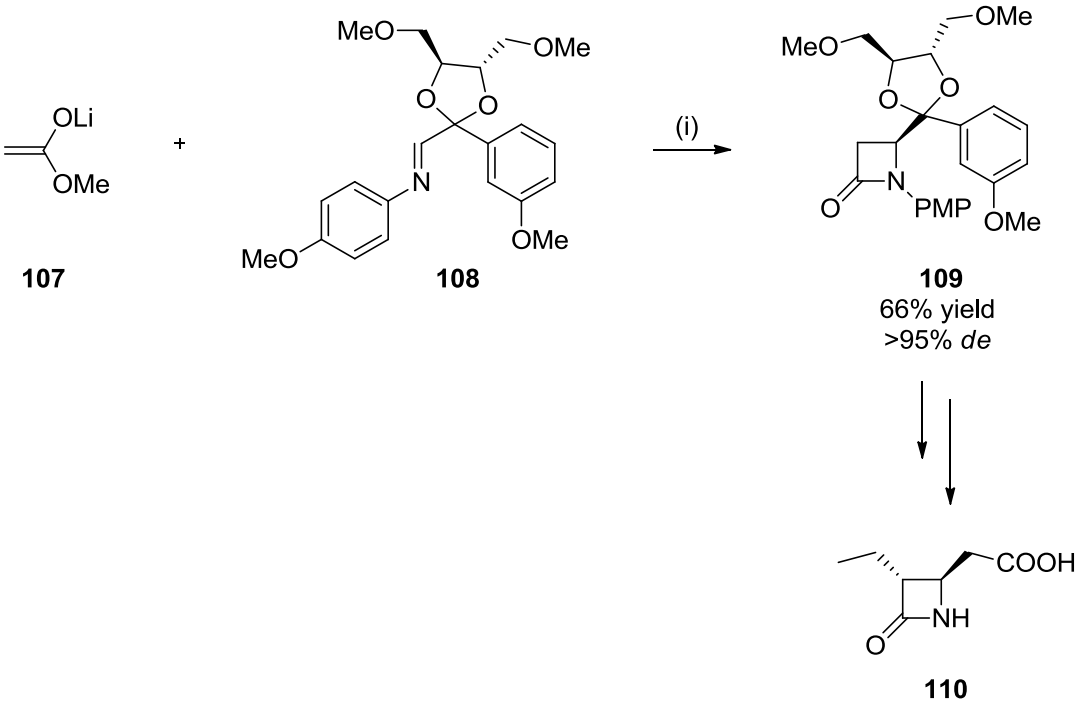
The first reported attempt at utilizing chiral imine components in ester-enolate imine cyclisation reactions were described using zinc enolates as nucleophiles which resulted in relatively poor diastereoselectivity.[59] However, this methodology was more successfully utilized for the synthesis of monosubstituted β-lactam **106** which was prepared with good stereocontrol due to formation of a chelated transition state between the (*E*)-enolate of **29** and α-cyano amine **105**.[31]



Scheme 38- β-lactam synthesis using chiral α-cyano amines[31]

Early results also showed that β-lactams could be formed in good *ee* using either tin[60] or boron[61] enolates, however these reactions resulted in the formation of β-amino ester products that required subsequent cyclisation to afford the desired β-lactam.

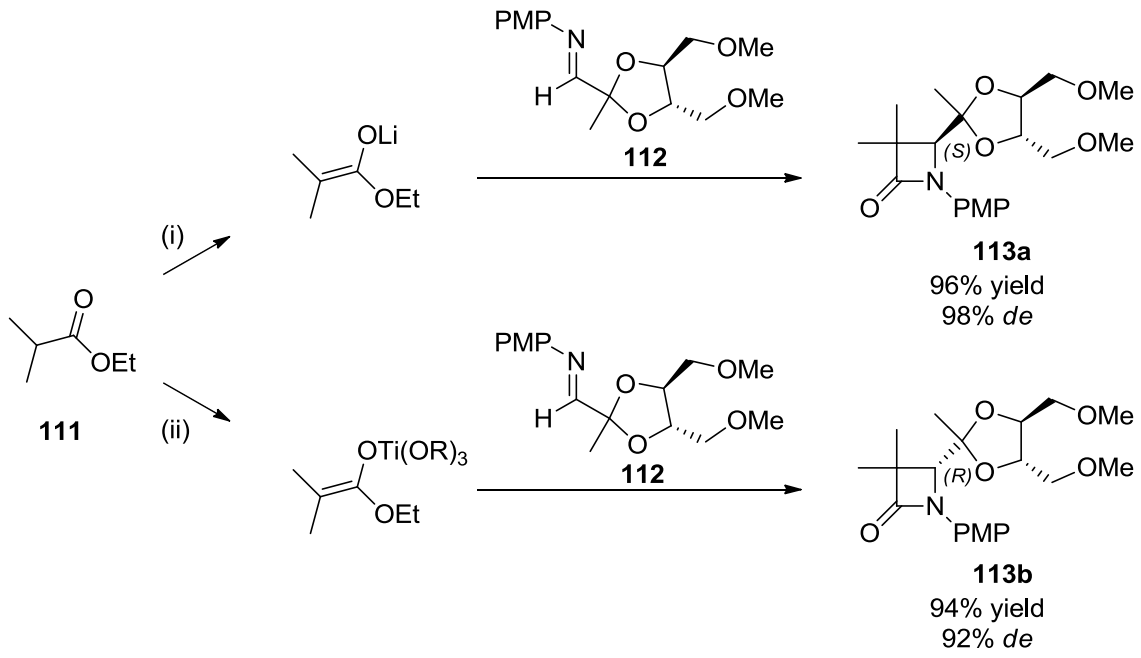
In 1992, a bulky chiral imine containing an acetonide functionality was employed for the asymmetric synthesis of mono-substituted β-lactams. Lithium enolate **107** was added to the chiral imine acetal **108** to give *trans*-β-lactam **109** in 66% yield with high diastereoselectivity.[62] The absolute configuration was determined by subsequently converting **109** into the *trans*-β-lactam **110**, that had been used previously as an intermediate for the synthesis of the antibiotic (+)-PS-5.[62]



Reagents & Conditions: (i) THF, -70°C

Scheme 39- Synthesis of (+)-PS-5 intermediate using chiral imines[62]

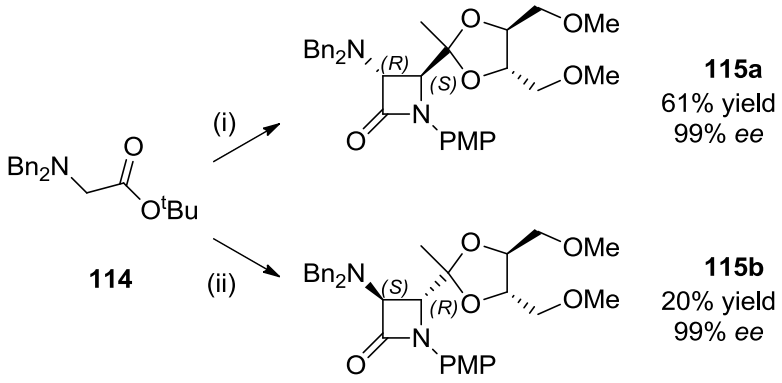
Further to this study, the ability to selectively access either enantiomer of a mono-substituted β-lactam **113** has been reported. In this study, the generation of lithium or zinc enolates with the (*S*,*S*)-tartrate derived imine **112** affords (4*S*)-β-lactam **113a**, whilst a titanium enolate resulted in the (4*R*)-β-lactam **113b** being observed.[63]



Reagents & Conditions: (i) LDA, DME, -78°C to rt, 12hrs; (ii) Ti(O^{i}Pr)$_3$Cl, Et$_2$O, -78°C to rt, 12hrs

Scheme 40- Effect of metal enolates on stereochemistry of β-lactam formation[63]

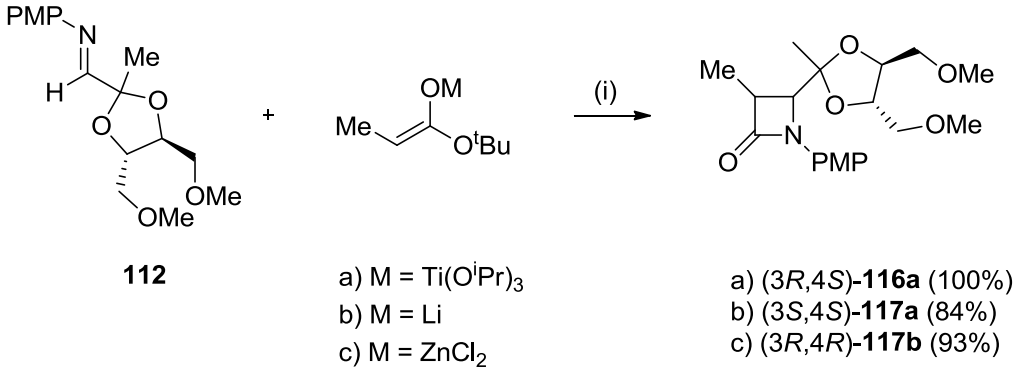
This method was further extended to the synthesis of β-lactams containing two contiguous stereocentres that incorporate a C3 amino substituent. The zinc enolate of *N*-protected *tert*-butyl glycinate **114** was reacted with chiral imine **112** affording (3*R*,4*S*)-β-lactam **115a**, whilst its corresponding titanium enolate afforded (3*S*,4*R*)-β-lactam **115b**.[64]



*Reagents & Conditions: (i) Ti(O^{i}Pr)$_3$Cl, THF, chiral imine **112**, -78°C to -40°C, 12hrs; (ii) ZnCl, THF, chiral imine **112**, -78°C to -40°C, 12hrs*

Scheme 41- Control of stereochemistry for C3-amino β-lactams using different metal enolates[64]

The effect of different metal enolates on the outcome of the stereochemistry of β-lactams when using a chiral imine was subsequently employed to synthesise all four diastereomers of 3,4-dialkyl-substituted β-lactams in good yield and high *de*.[65] The (3*S*,4*R*)-β-lactam **116b** was obtained by epimerization of the corresponding (3*S*,4*R*)-β-lactam **116a**.



112

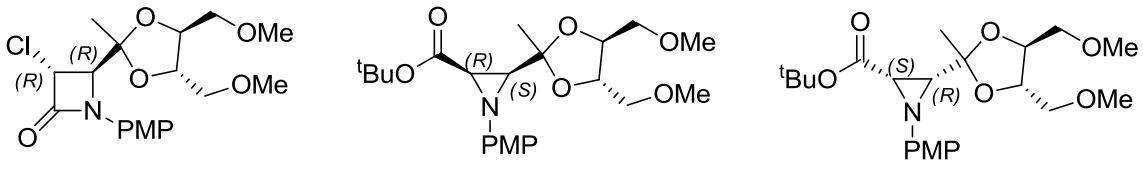
a) M = Ti(O^{i}Pr)$_3$
b) M = Li
c) M = $ZnCl_2$

a) (3*R*,4*S*)-**116a** (100%)
b) (3*S*,4*S*)-**117a** (84%)
c) (3*R*,4*R*)-**117b** (93%)

Reagents & Conditions: a) & b) (i) HMPA (12 equiv.), -78 °C to -60 °C; c) i) -78 °C to rt

Scheme 42- Effect of different metals on the stereochemical outcome of β-lactam synthesis

In contrast, the products formed from reaction of ester enolates of α-chloroacetates with chiral imines are dependent on the nature of the enolate counterion, with a titanium enolate affording (3*R*,4*R*)-3-chloroazetidine-2-one **118**, whereas lithium or zinc enolates afford the alternative (2*R*,3*S*)- or (2*S*,3*R*)-aziridines **119** respectively.[66]

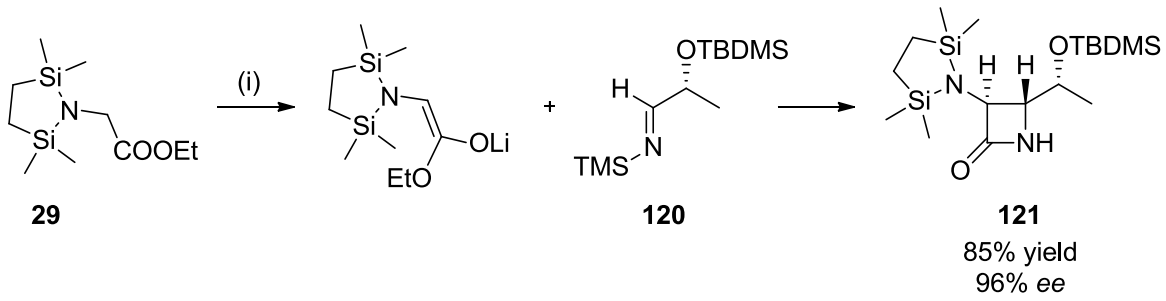


118 **119a** **119b**

Figure 5- Products of reaction of metal enolates of α-haloacetates with a chiral imine[66]

The synthesis of enantiopure 3-amino-4-(1'-*O*-silyl)-substituted monocyclic β-lactams was first reported *via* reaction of achiral ester enolate **29** with a chiral silylimine **120**.[67] The *trans*-selectivity observed in Scheme 43 has been rationalized by recent studies,

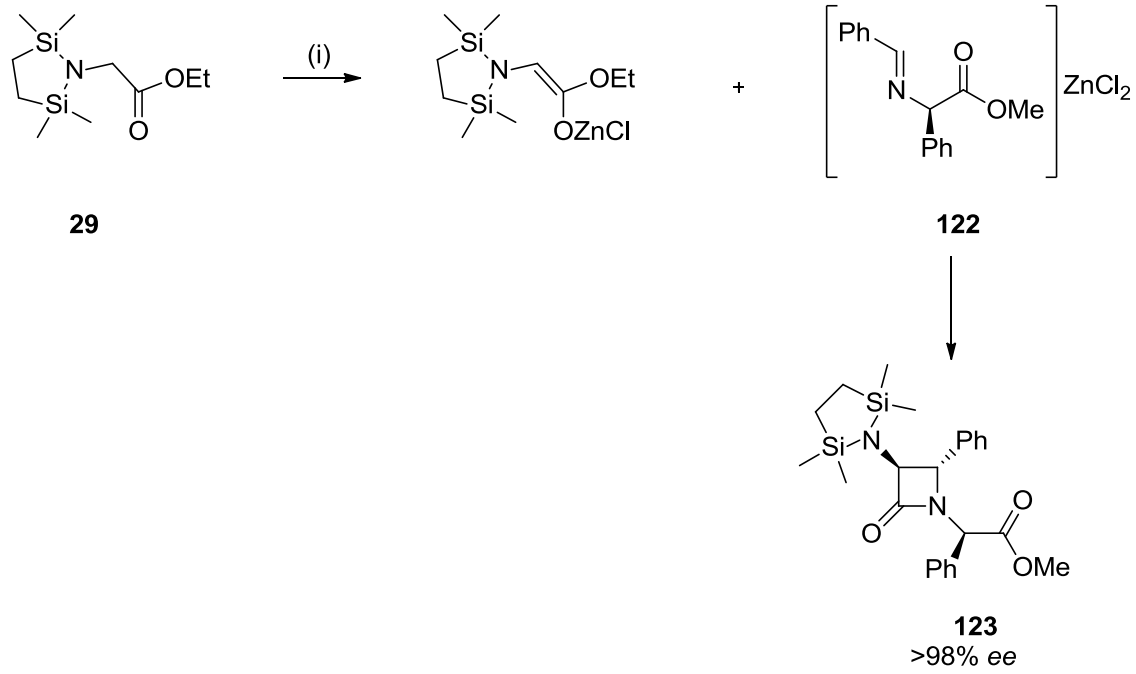
which suggests the *trans*-configuration is observed when the α-imine substituent is bulky.[67]



Reagents & Conditions: (i) LDA, -78°C, THF

Scheme 43- Synthesis of 3-amino-4-(1'-hydroxy)-substituted β-lactams[67]

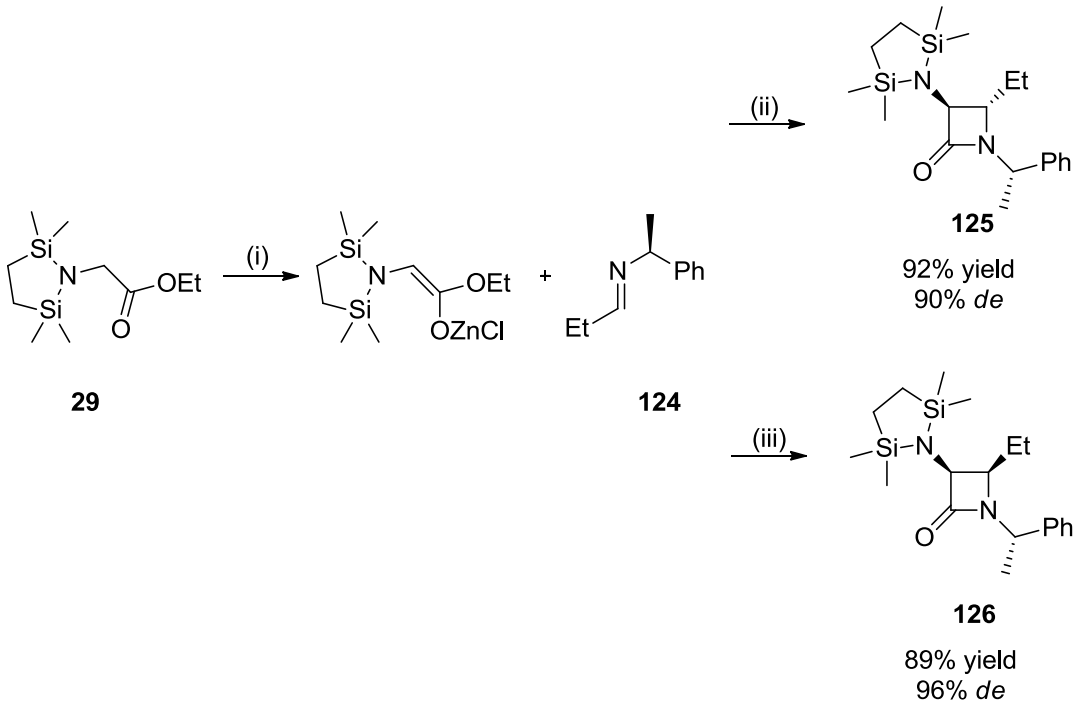
The ability to employ chiral substituents on the nitrogen atom was explored by incorporating chiral α-amino acids into the imine starting material. It was reported that the double activation of both enolate of ester **29** and imine **122** was necessary for the zinc enolate to cyclise, which furnished the (3*S*,4*S*)-β-lactam **123** in good yield and high *ee*.[68-69]



Reagents & Conditions: (i) LDA, $ZnCl_2$

Scheme 44 β-lactam formation from double zinc activation of enolate and imine components[68]

It has been established that the use of zinc enolates for the ester enolate-imine cyclisation reaction normally favours the formation of *trans*-β-lactams. Consequently, an investigation was undertaken to examine the variables that could potentially encourage formation of the corresponding *cis*-β-lactam from reaction of enolates of ethyl 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane-1-acetate with *N*-alkyl imines. The factor that showed the most significant effect on changing the *cis*-*trans*-diasteromeric ratio was the addition of a highly polar cosolvent, with TMU, DMPU and HMPA markedly increasing the amount of *cis*-β-lactam **126** formed. For example, reaction of the zinc enolate of **29** with a chiral imine **124** derived from α-methylbenzylamine gave *trans*-(3*S*,4*S*)-β-lactam **125** in 95% *de* with a 92% yield (Scheme 45),[70] whilst addition of HMPA resulted in formation of the corresponding *cis*-isomer **126** as the major product.[15,70]



29 **124**

Reagents & Conditions: (i) a) LDA, Et_2O; b) $ZnCl_2$; (ii) -78°C to rt, H_2O; (iii) HMPA, THF, -78°C

Scheme 45- Effect of cosolvent HMPA on *cis*:*trans* selectivity[70,15]

The ability to prepare β-lactams containing two new contiguous stereocentres *via* enolate-imine condensation reactions has been widely investigated by Cainelli *et al.*[16] It was demonstrated that changing the nature of the enolate counterion and the nature of

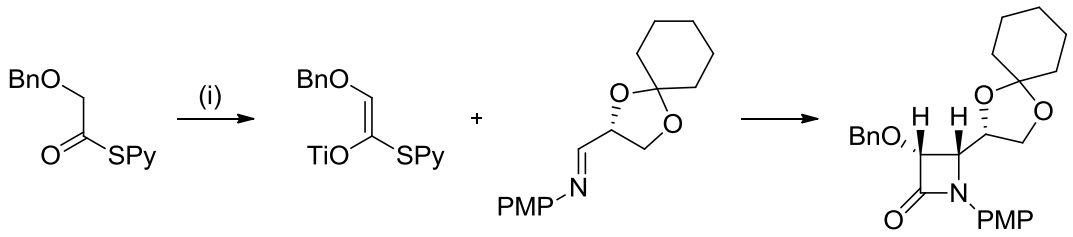
the *O*-protecting group on the imine affected the stereochemical outcome of the reaction. The presence of a bulky *O*-silyl substituent within the imine results in formation of the *trans* β-lactam in high *ee*. As seen in Scheme 46, altering the imine substituent from a methyl **128** to a phenyl **129** fragment resulted in an increase in the *ee* of β-lactam from 92% (**130**) to >98% (**131**).

127 **128** R= Me, **129** R= Ph

130 R= Me: 63% yield, 92% *de*
131 R= Ph: 84% yield, >98% *de*

Scheme 46- Effect of imine substituents on stereoselectivity of β-lactam formation[16]

An investigation into the effects of reacting enolates of 2-pyridyl thioesters with different chiral imines has been undertaken by Annunziata *et al.* who demonstrated that the titanium enolate of thioester **64** reacted with imine **132** to afford the *cis*-β-lactam **133** in >98% *de* (Scheme 47).[71] In light of this accomplishment, β-lactam **133** was further developed as a potential precursor for the synthesis of a biologically active renin inhibitor.[72]



64 **132** **133**

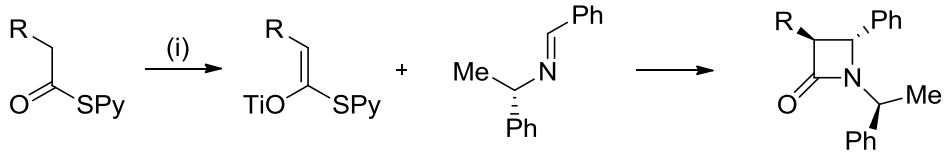
82% yield
>98% *de*

Reagents & Conditions: (i) $TiCl_4$, Et_3N, DCM, -78°C to 0°C, 3hrs

Scheme 47- Stereoselective synthesis of *cis*–β-lactams using a chiral imine[71]

Imines derived from α-substituted benzylamines react with titanium enolates of 2-pyridyl thioesters to give *trans* β-lactams in good yield and high selectivity as shown in Scheme 48.[73] The selectivity of these reactions was rationalized using a transition state

involving coordination of titanium to both the enolate and the 2-pyridyl group,[74] with improved stereocontrol occurring as the steric demand of either the imine or thioester substituent increases.[73]

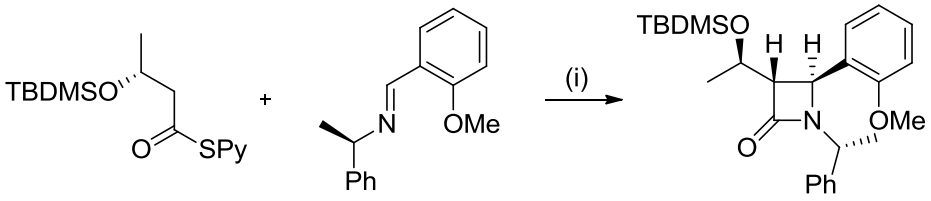


134 **135** R= Et (79% yield, 86% *de*, 60% *ee*)
136 R= ^{i}Pr (62% yield, 86% *de*, 82% *ee*)

Reagents & Conditions: (i) $TiCl_4$, Et_3N, DCM, -78°C to 0°C, 5hrs

Scheme 48- Use of α-methylbenzylamine as a chiral auxiliary for imine formation

In contrast, when the matched enolate-imine condensation reaction between the titanium enolate of chiral thioester **137** and chiral imine **138** was carried out, then a highly stereoselective reaction was observed, yielding the *trans* (3*S*,4*S*)-β-lactam **139** in high *de*.[75]



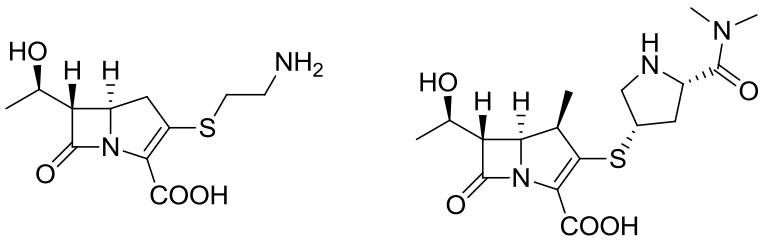
137 **138** **139**

83% yield
>98% *de*
>98% *ee*

Reagents & Conditions: (i) $TiCl_4$, Et_3N, DCM, -78°C to 0°C, 5hrs

Scheme 49- Matched stereocontrol using a titanium enolate of chiral thioester and a chiral imine[75]

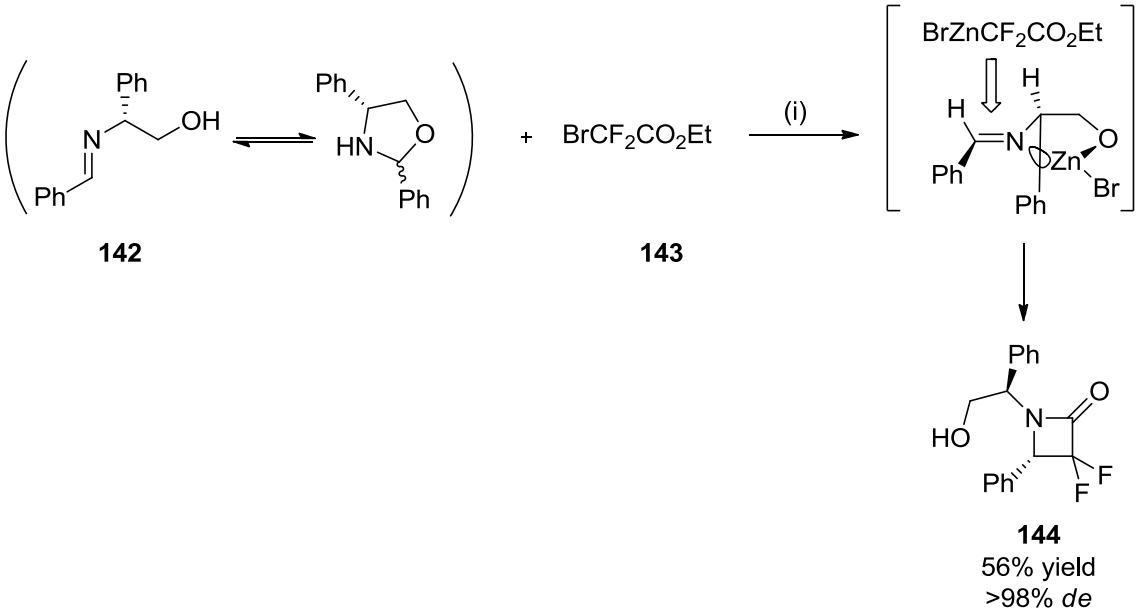
This excellent level of stereocontrol enabled a variety of different functional groups to be introduced, furnishing substrates that could be employed for the synthesis of carbapenem antibiotics, including thienamycin substrate derivatives.[75]



140 **141**

Figure 6- Structures of Thienamycin 140 and Meropenem 141

More recently in 2007, Boyer *et al*[76] demonstrated that zinc enolates could be used to prepare (*rac*)-*gem*-difluorinated β-lactams **144** under standard Refomatsky conditions as potential metallocarboxy-peptidase inhibitors.[77] The stereochemical outcome of this reaction could be controlled using (*R*)-phenylglycinol **142** as a chiral auxiliary, this enables chelation between the nitrogen and the zinc alkoxide to afford a five membered transition state, resulting in excellent diastereoselectivity.[76]



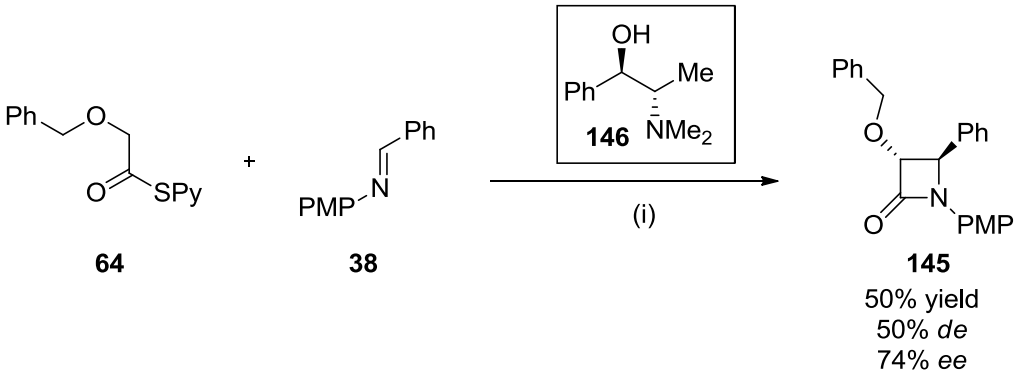
142 **143** **144**
56% yield
>98% *de*

Reagents & Conditions: (i) Zn, THF, reflux, 2hrs

Scheme 50- Synthesis of *gem*-difluoro-β-lactams *via* a Reformatsky reaction[76]

1.6 Enantioselective Synthesis - External Ligands

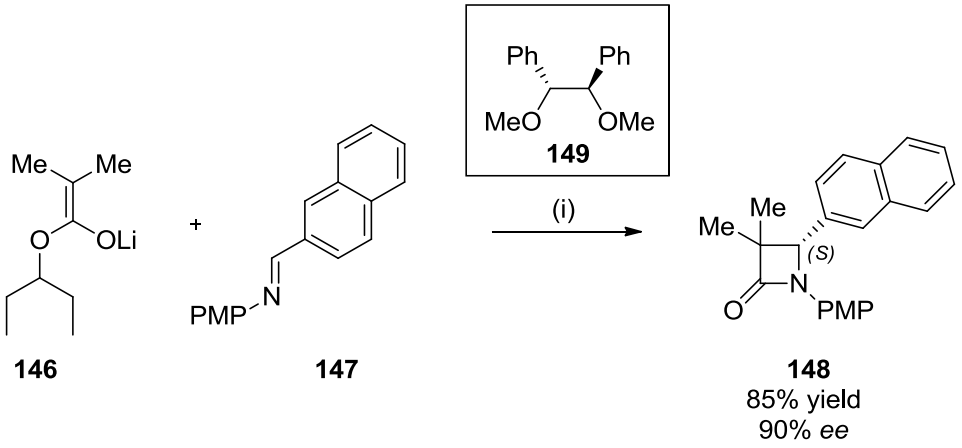
A number of protocols have been developed that enable stoichiometric amounts of external chiral ligands to be used as promoters to carry out the asymmetric synthesis of β-lactams from achiral ester/imine starting materials. Boron enolates have been shown to afford *cis*-β-lactams with good levels of stereocontrol,[78] which enabled an enantioselective ester enolate-imine cyclisation reaction to be developed using a stoichiometric amount of the chiral additive (1*R*,2*S*)-2-(dimethylamino)-1-phenylpropan-1-ol.[79] The chiral amino alcohol additive **146** acts both as a base to generate a boron enolate, as well as acting as a chiral ligand to coordinate to BCl_3 to generate a chiral Lewis acid species that facilitated the enantioselective synthesis of *trans*-β-lactam **145** in 74% *ee* (Scheme 51).[79]



*Reagents & Conditions: (i) [$BCl_3.Me_2S$ + chiral amino alcohol **146**], DCM, -78°C to rt*

Scheme 51- Effect of boron halide adduct as Lewis acids on absolute stereochemistry[79]

In addition, (1*R*,2*R*)-1,2-dimethoxy-1,2-diphenylethane **149** has been used as a chiral ligand to coordinate the lithium counterion of ester enolate **146**,[80] to afford β-lactam **148** in 85% yield and 90% *ee* (Scheme 52).



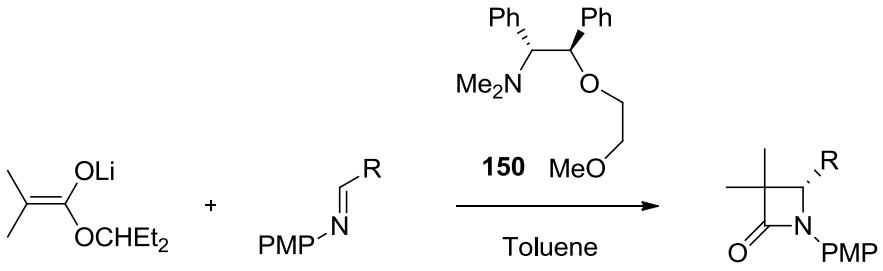
146 **147** **148**
85% yield
90% *ee*

*Reagents & Conditions: (i) LICA, ligand **149**, toluene, -50°C*

Scheme 52- The effect of an external chiral ligand on β-lactam synthesis[80]

These reaction conditions were further optimised using (1*R*,2*R*)-2-(2-methoxyethoxy)-*N*,*N*-dimethyl-1,2-diphenylethanamine **150** as a ligand, in addition to altering the different aromatic substituents on the imine substrate, which enabled a range of chiral β-lactams to be prepared in high yields and high enantioselectivites.[81]

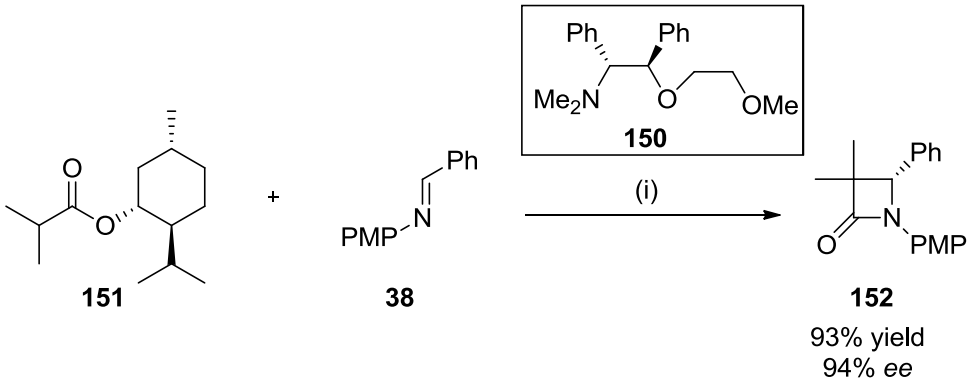
Table 3- "Matched" condensation of enolate 146 with imines catalysed by (1*R*,2*R*)-2-(2-methoxyethoxy)-*N*,*N*-dimethyl-1,2-diphenylethanamine 150 forming β-lactams



146

Entry	R	Yield (%)	*ee* (%)
1	Ph	99	89
2	PMP	99	90
3	2-Naphthyl	99	88
4	CMe=CHPh	99	82

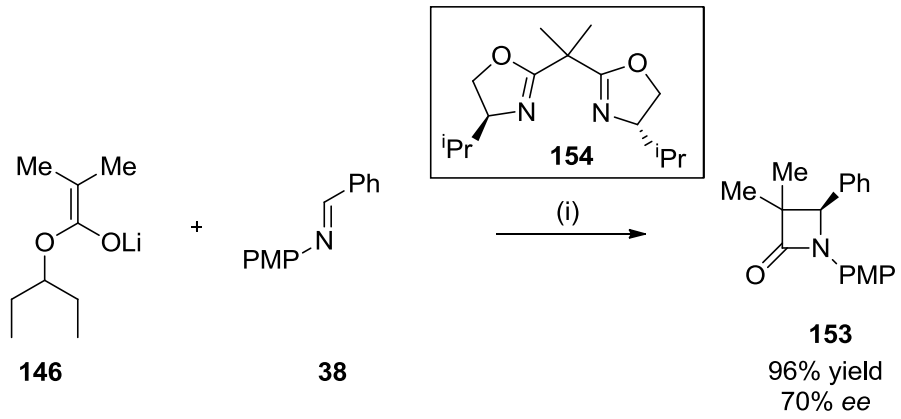
The stereoselective synthesis of β-lactam **152** was enhanced by addition of the chiral ether ligand **150** to the lithium enolate of menthyl isobutyrate. A catalytic amount of the chiral tridentate ligand significantly increased the enantiomeric excess from 50% to 94% *ee*.[82] Furthermore, changes made to the structure of the chiral ligand, or the chiral lithium enolate, enabled either β-amino ester or β-lactam products to be obtained.[82]



*Reagents & Conditions: (i) LDA, ligand **150**, toluene, -35°C, 12hrs*

Scheme 53- Matched effect of chiral lithium enolates & chiral external ligands[82]

In light of this success, investigations employing chiral bisoxazoline (BOX) ligands for use with achiral lithium ester enolates were reported,[83] with the best conditions being obtained when 20 mol% of the BOX ligand containing an isopropyl substituent **154**, was employed, giving β-lactam **153** in 96% yield and 70% *ee* (Scheme 54).[83]

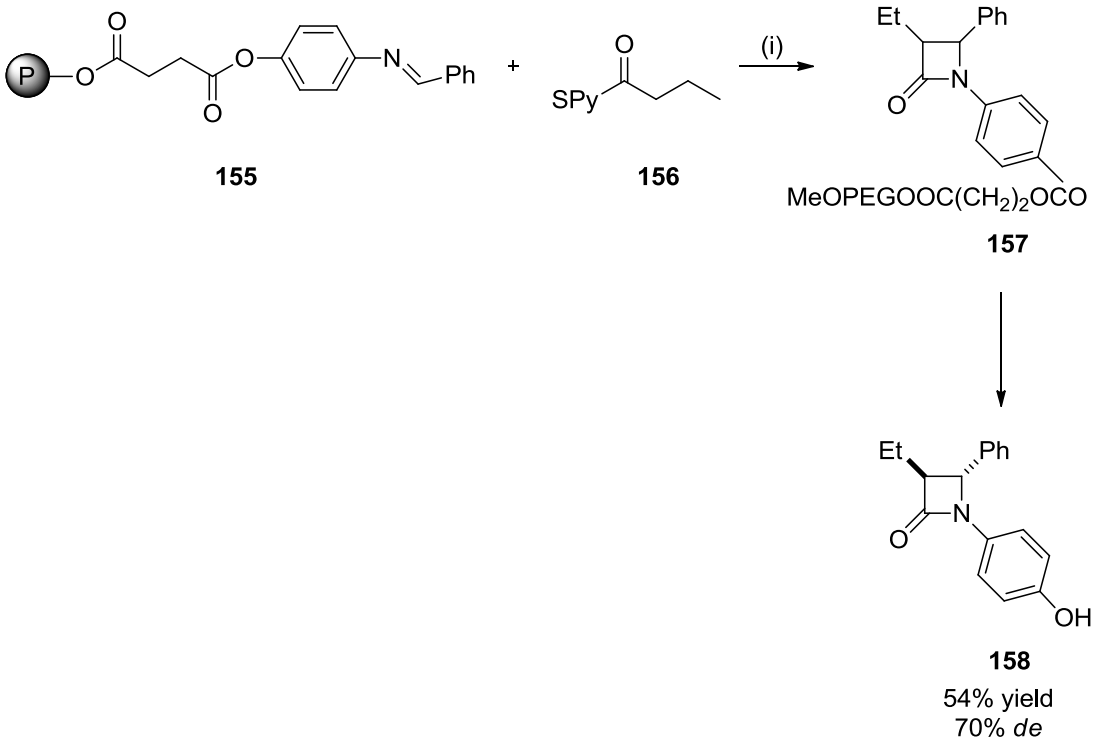


*Reagents & Conditions: (i) Ligand **154** (0.2 equiv.), toluene, -20°C, 4hrs*

Scheme 54- Controlling β-lactam formation using chiral bisoxazoline (BOX) ligands[83]

1.7 Polymer Supported β-Lactam Synthesis

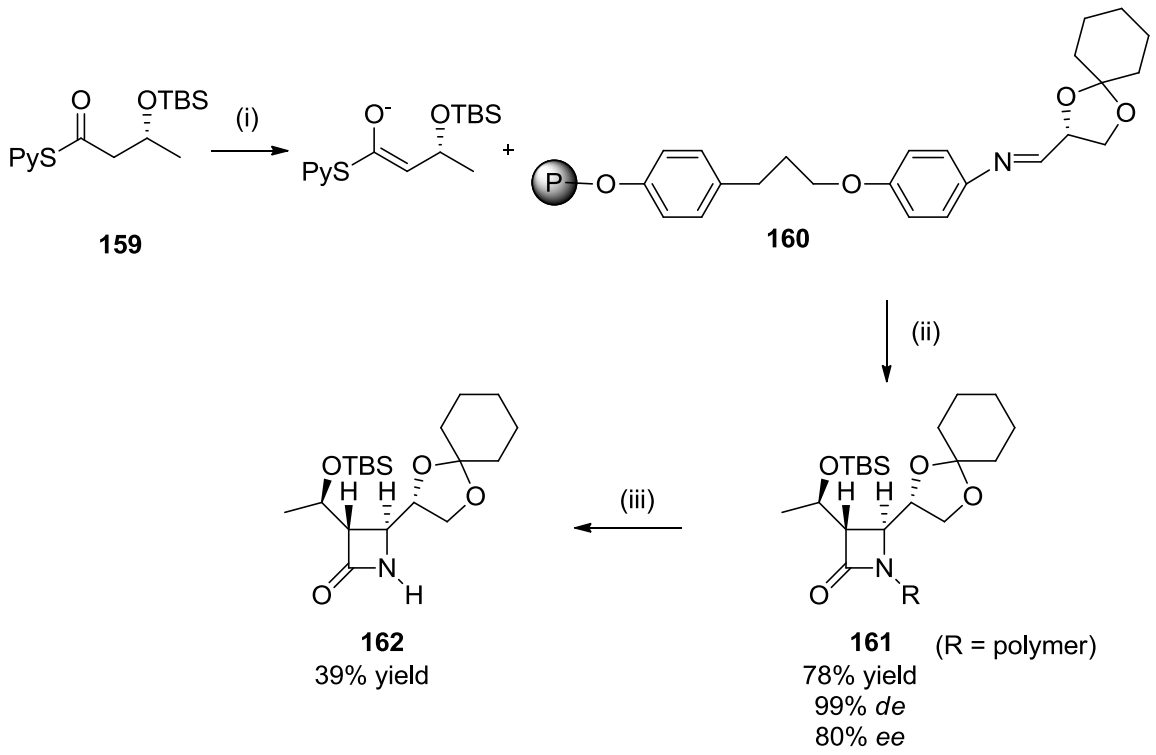
A number of approaches have been developed that enable the ester enolate-imine cyclisation reaction to be transferred to polymer support potentially allowing for the high-throughput synthesis of libraries of β-lactams.[84] The first polymer-supported synthesis of a β-lactam was reported in 1998, whereby an imine **155** was immobilized *via* a soluble MeOPEG (poly(ethylene glycol)) bound linker which was reacted with a titanium enolate to afford the β-lactam **157**.[85] The linker was removed by acid catalysed methanolysis of the polymer bound β-lactam **158** to give the free β-lactam in 54% yield.[85]



Reagents & Conditions: (i) $TiCl_4$, Et_3N, DCM, 23°C, 15hrs

Scheme 55- Synthesis of β-lactams on polymer supported imines[85]

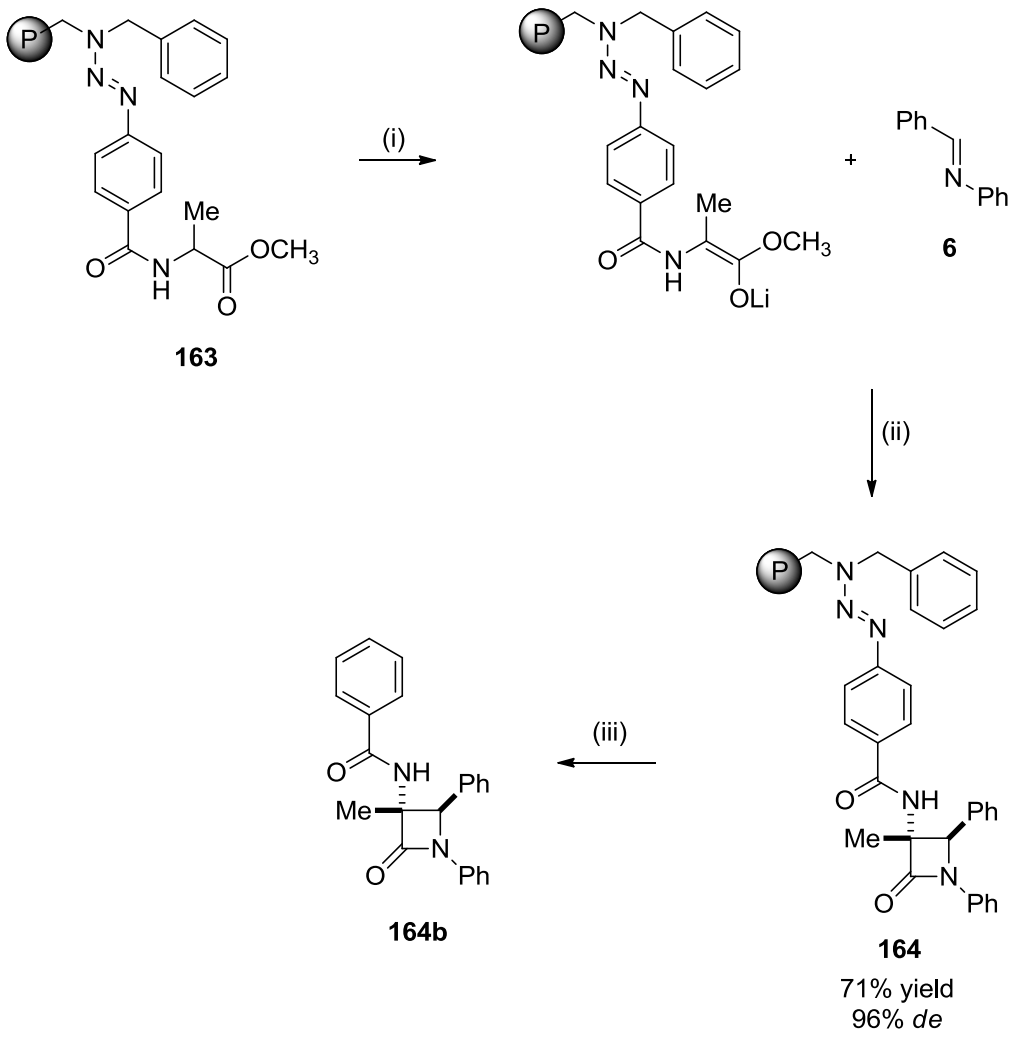
A modified PEG support was subsequently employed to prepare an immobilized chiral imine **160** that was reacted with the titanium enolate of a chiral thioester **159** to generate the *trans*-β-lactam **161** in good *ee*.[86]



Reagents & Conditions: (i) $TiCl_4/(C_8H_{17})_3N$ (ii) DCM, -78°C to rt, 2hrs; (iii) CAN, MeCN:H_2O, -30°C, 2hrs

Scheme 56- Enantiomerically pure immobilized imine and enolate in β-lactam formation[86]

An alternative strategy has been devised by Schunk *et al.* involving immobilisation of the ester functionality to polymer support using a T1-triazine linker that is stable under basic conditions.[87] Subsequent generation of the lithium enolate of the polymer-supported ester **163**, followed by reaction with a range of imines and cleavage from polymer support gave a series of eight *cis*-β-lactams in excellent *de* and good yields.[87] The full potential of this immobilized ester enolate methodology was subsequently demonstrated for the synthesis of a variety of libraries of β-lactams.[88]



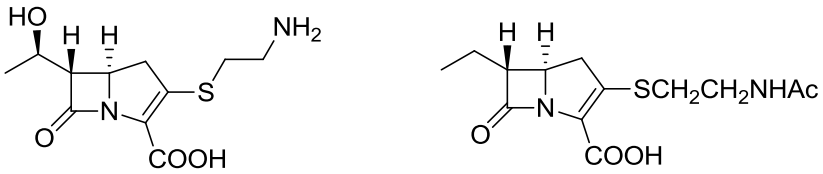
Reagents & Conditions: (i) LiHMDS, THF, -78°C, 20 mins; (ii) -78°C to rt, 23hrs; (iii) a) 5% TFA, DCM; b) THF/DMF, 60 °C, 15 min

Scheme 57- Synthesis of β-lactams using an immobilised titanium ester enolate[87]

However, the incorporation of a chiral auxiliary onto the polymer supported ester in order to control the enantioselectivity of the β-lactam has yet to be reported.

1.8 Natural Product & Antibiotic Synthesis

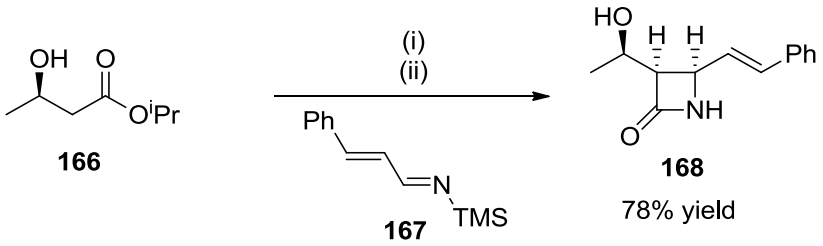
The ability of the enolate-imine condensation reaction to produce β-lactams in both high *de* and *ee* for a variety of highly substituted analogues has led to its use for the synthesis of a wide range of complex natural products. Many antibiotics contain the β-lactam moiety as their key feature and as such this methodology can be utilized to provide access to many of the biologically important targets. Initially, there was a large focus on employing β-hydroxybutyrates as the chiral ester component within the enolate-imine condensation reaction, as these types of substrates could potentially provide an enantioselective route to carbapenem antibiotics, such as thienamycin **140**.[14]



140 **165**

Figure 7- Structure of Thienamycin 140[89] and antibiotic PS-5 165

One of the most significant developments involved reaction of the zinc enolate of β-hydroxybutyrate **166** with imine **167** which generated β-lactam **168** in 78% yield as the only stereoisomer, this was proposed to proceed *via* a chelated transition state involving an (*E*)-enolate and the imine (Scheme 58).[90]

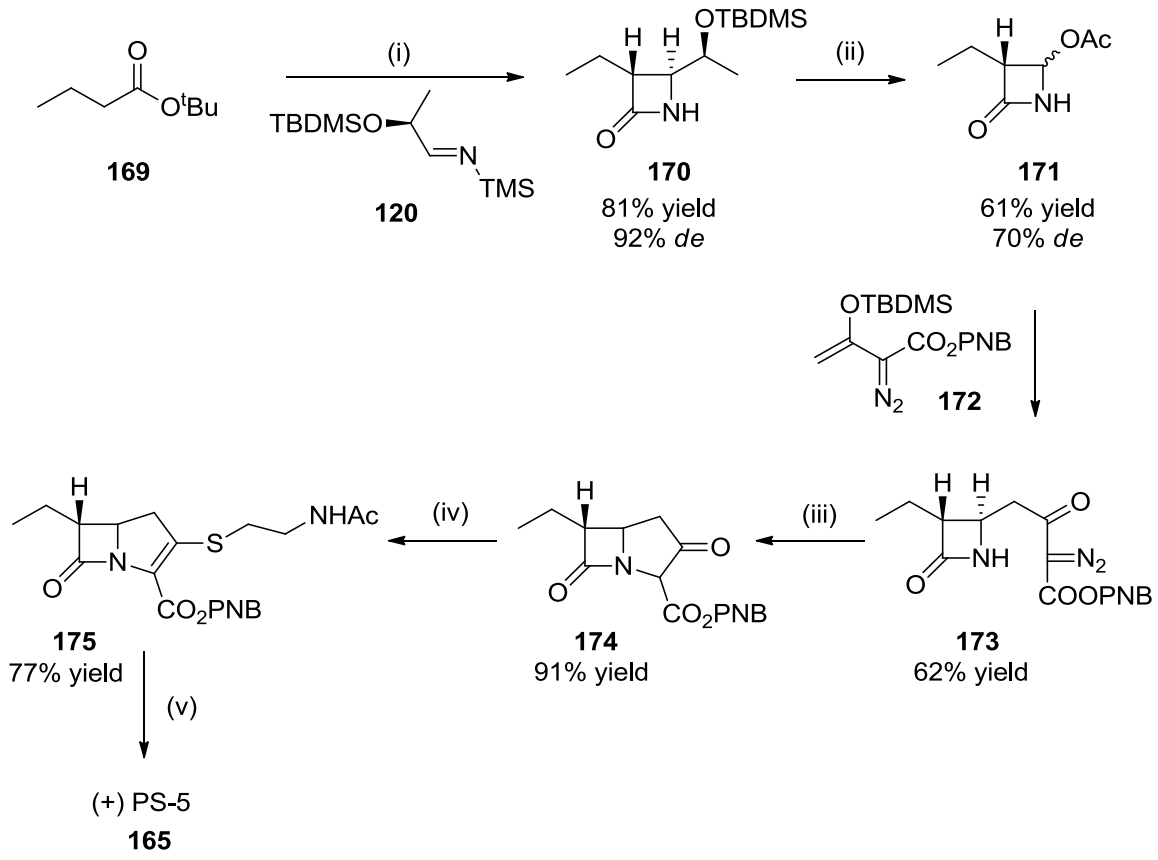


Reagents & Conditions: (i) Et_2Zn; (ii) LiHMDS, THF

Scheme 58- Synthesis of β-lactams using chiral β-hydroxybutyrate 166[90]

The condensation of β-hydroxybutyrate enolates with *N*-aryl imines and *N*-trimethylsilyl imines is well documented, reporting good yields with the stereoselectivity highly dependent on the chosen reaction conditions.[14]

In addition, early work was also directed towards the synthesis of β-lactam **171** as an intermediate for the synthesis of the structurally related antibiotic PS-5 **165**. The aim was to synthesise 4-acetoxy β-lactams *via* an enantioselective enolate-imine condensation reaction[91-92] involving the addition of lithium ester enolate **169** to a chiral imine **120** to give the *trans*-β-lactam **170** in good *de*, which was subsequently converted into the 4-acetoxy β-lactam **171** in 61% yield.[67] A synthesis employing 4-acetoxy β-lactam **171** had previously been reported and therefore enables a formal synthesis of (+)-P5-5 **165** (Scheme 59).[93]

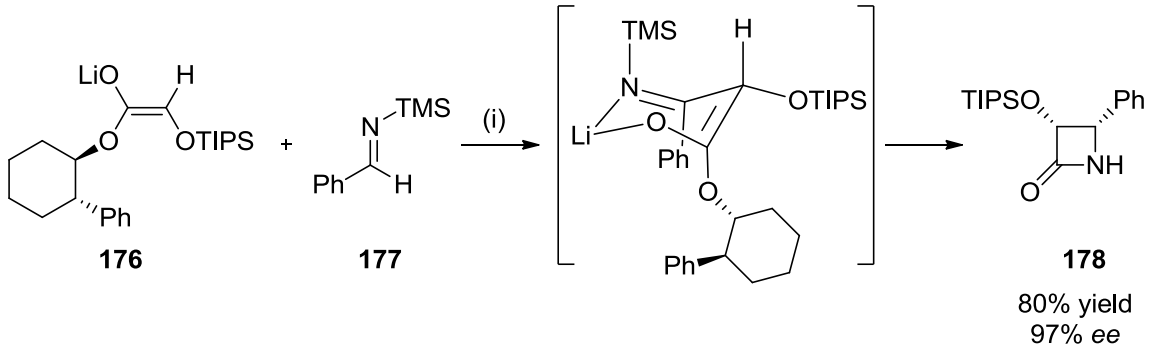


Reagents & Conditions: (i) LDA, THF; (ii) a) TBAF, MeCN; (b) $Pb(OAc)_4$, benzene, reflux; (iii) 1,2-DCE, $Rh_2(OAc)_4$; (iv) $(ClP(O)(OC_6H_5)_2$, iPr_2NEt, MeCN, N-acetylcysteamine; (v) H_2, Pd/C, THF

Scheme 59- Synthesis of 4-acetoxy β-lactams for PS-5 synthesis[92-93]

In 1991, the asymmetric synthesis of chiral β-lactam building blocks that could be incorporated into the construction of the side chain of the anti-cancer agent taxol was successfully developed. Both high yield and high *ee* were obtained for formation of *cis*-

β-lactam **178** using a lithium chiral ester-enolate condensation reaction with *N*-TMS-imine **177**, that employed a (-)-*trans*-2-phenyl-1-cyclohexyl chiral ester fragment for diastereocontrol.[94] This methodology was also employed for the generation of a series of taxol analogues with modified C-13 side chains.[95]



Reagents & Conditions: (i) LDA, THF, -78°C

Scheme 60- Asymmetric synthesis of β-lactam 178 for use as taxol C-13 side chain[94]

The use of this type of ester enolate-imine condensation reaction to incorporate heteroatom substituents into the parent β-lactam enabled the synthesis and biological evaluation of a range of heteroaromatic taxanes, some of which were shown to be more cytotoxic against B16 melanoma cells than paclitaxel **179**.

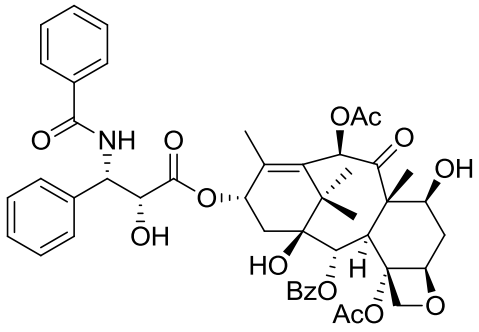
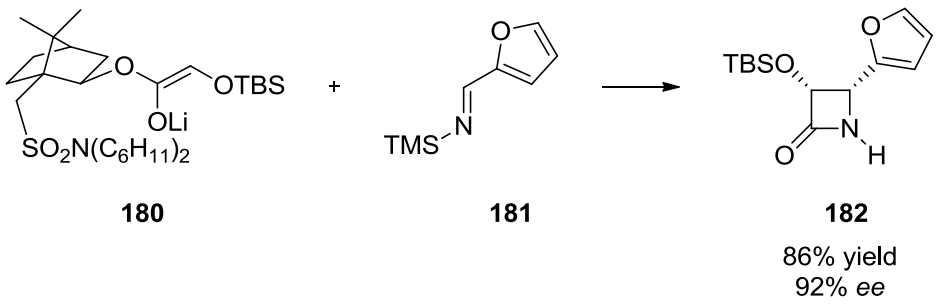


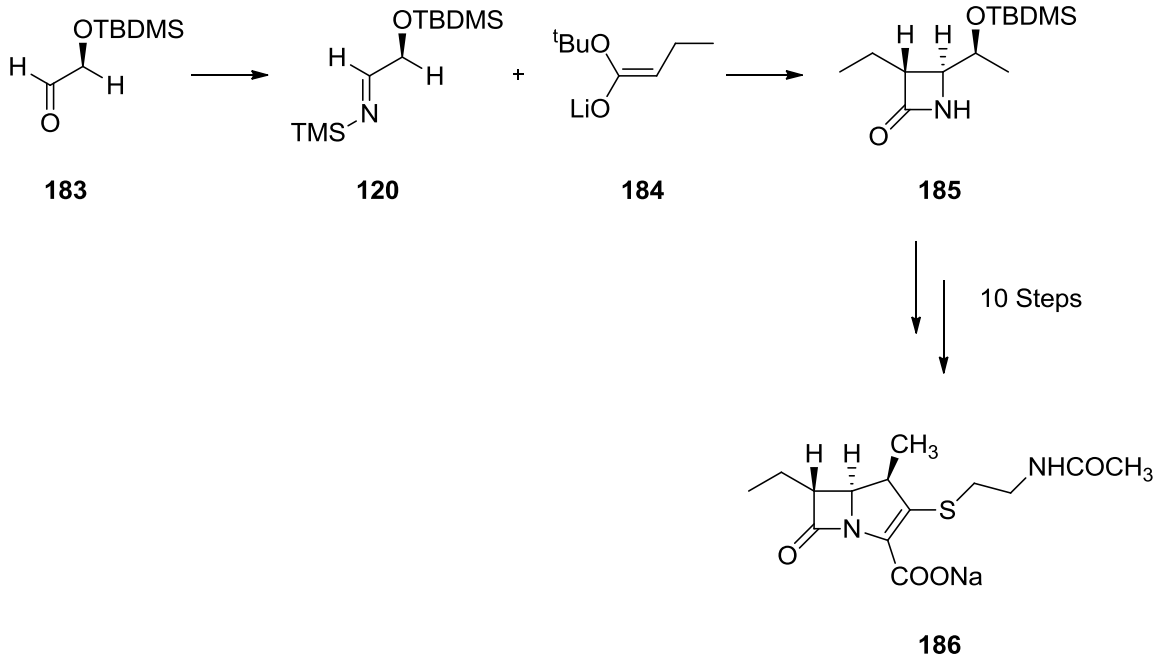
Figure 8- Structure of Paclitaxel 179

For example, the reaction of a chiral lithium enolate **180** with *N*-TMS-imine **181** gave the *cis*-2-furyl substituted β-lactam **182** in high *ee*.[96]



Scheme 61- Synthesis of 2-furyl substituted β-lactams for incorporation into heteroaromatic taxanes[96]

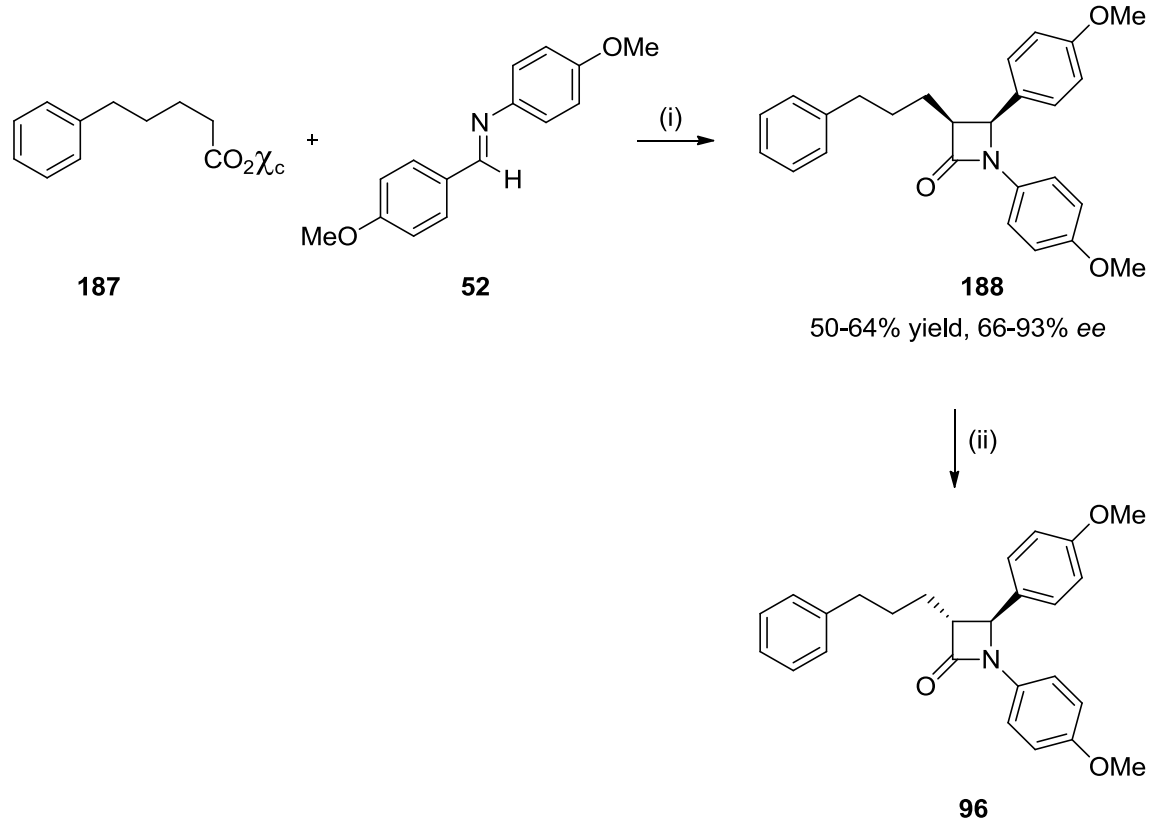
In 1993, Bandini *et al*. demonstrated that it was possible to synthesise the β-lactam antibiotic (+)-1β-methyl PS-5 **186**, by employing the ester enolate-imine condensation reaction as the pivotal β-lactam ring-forming step.[97] The use of chiral imine **120** enabled the synthesis of an enantiomerically pure 3,4-disubstituted *trans*-β-lactam **185** that was subsequently converted into the carbapenem antibiotic (+)-1β-methyl PS-5 **186**.[97]



Scheme 62- Synthesis of (+)-1β-methyl PS-5 *via* an ester enolate-imine condensation recation[97]

The first asymmetric synthesis of SCH 48461 **96**, a proven cholesterol absorption inhibitor, could also be carried out using an ester-imine condensation that employed a

chiral ester fragment to introduce stereocontrol.[98] Four different chiral auxiliaries were investigated including D/L-menthol and (+)/(-)Oppolzer's chiral auxiliary with *ee*'s of up to 93% being obtained.[98] This *cis*-β-lactam **188** was then epimerized under basic conditions to give the corresponding *trans*-(3*S*,4*S*)-β-lactam **96** in quantitative yield. HMPA was employed as an additive during the enolate-imine condensation reaction in an attempt to directly afford the *trans*-β-lactam, however these conditions led to a complete loss of stereocontrol.[98] Furthermore, this methodology could be used to prepare a series of analogues of SCH 48461 **96** in order to determine the structure-activity relationships of the azetidinone fragment.[99]



Reagents & Conditions: (i) LDA, THF, -78°C, (ii) KO^{t}Bu, THF

Scheme 63- Asymmetric synthesis of cholesterol absorption inhibitor SCH 48461[98]

This ester-imine condensation methodology allowed access to a series of *N*-alkyl and *N*-acyl-2-β-lactams, which led to the conclusion that the alkoxy group on the *N*-substitued aromatic ring was not required for its pharmacological effect.[99]

1.9 Conclusion

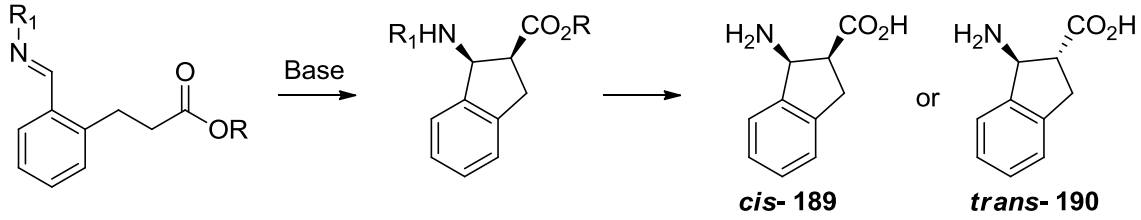
The ester enolate-imine condensation reaction has long been considered one of the main methods for the synthesis of β-lactams. Control of the reaction conditions and appropriate selection of the metal enolate can be used to selectively alter the *trans*:*cis* ratio of the resultant β-lactam. In addition, the introduction of a chiral auxiliary into either the ester or imine functionality has the potential to afford asymmetric syntheses of a diverse range of substituted β-lactams. The use of this methodology for the asymmetric synthesis of antibiotics and biologically active substrates has been demonstrated highlighting the potential of this reaction for total synthesis.

2 Results & Discussion – Development of an Intramolecular Enolate-Imine Cyclisation Reaction for the Synthesis of Benzocispentacin

2.1 Introduction

The ability to synthesise a range of enantiomerically pure β-amino acids is essential to allow access to a variety of β-peptide foldamer motifs.[100] Recent developments in the field of foldamer synthesis have led to a renewed interest in diversifying the number of β-amino acids available as building blocks for such scaffolds.[101] There are a range of existing methodologies for the asymmetric synthesis of simple cyclic β-amino acids containing a single stereocentre,[102-103] but methodologies for constructing cyclic β-amino acids that contain more than one stereocentre are much less advanced. An attractive approach is to generate β-amino acids that contain multiple stereocentres, in particular β-amino acid scaffolds containing aromatic substituents. They have the potential to encourage folding in oligoamides using secondary π–π stacking interactions[104] to afford foldamers that have a wide range of potential applications.

The original aim of the research project was to carry out a series of intramolecular enolate-imine cyclisation reactions, screening different chiral auxiliaries (R or R_1) to afford enantiopure cyclic β-amino acids such as *cis*-**189** or *trans*-**190** (Scheme 64). At the outset this involved the screening of a series of 5-*exo*-trig cyclisation reactions involving intramolecular nucleophilic attack of various enolates onto an imine with the stereochemistry controlled by an appropriate chiral auxiliary.



Scheme 64- Development of β-amino acid monomers for foldamer synthesis

2.2 Background - Foldamer Synthesis

In the past decade, a vast array of research has been carried out into the synthesis of foldamers with significant contributions from the groups of Gellman[105-106] and Seebach.[107-109] The detailed discussion of this area is beyond the remit of this chapter, but an understanding of the fundamental properties of this research area are key to understanding why cyclic β-amino acids are such desirable targets.

Generally, a foldamer is considered to be an artificially adopted structure that assumes specific conformations that replicate biological macromolecules. In their original report, Gellman *et al.* investigated backbones that favour helical secondary structures and defined foldamers as 'synthetic oligomers with unnatural backbones'(Figure 9).[110]

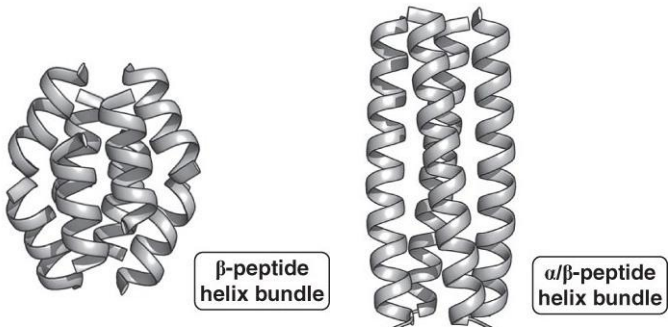


Figure 9- Examples of helix bundle quaternary structures[111]

Oligomers incorporating β-amino acids producing foldamers continue to be widely investigated,[112] due to the potential of β-peptides to modify biological activities.[113-114] The additional methylene unit allows extra conformational space that confers excellent folding properties within the β-peptide,[115] whilst they are also stable to proteolytic degradation.[116] The use of β-amino acids containing aromatic substituents can drive folding through π–π stacking interactions and favourable side chain-solvent contact in secondary and tertiary stuctures.[104,117] This enables reduction of destabilising backbone-solvent interactions while allowing relatively rigid conformations.[117] Such repeating units are not found in natural biomolecules as short range interactions in α-peptides are mainly observed through hydrogen bonding. More recently work has begun into designing heterogeneous backbone foldamers, consisting of both α and β-amino acid moieties which can afford additional different spatial orientations.[111,118]

In particular, Gellman *et al.*[119] have highlighted the use of *trans* β-amino acids such as *trans*-2-aminocyclohexanecarboxylic acid (ACHC) within β-peptides to generate 14-helical conformations. The helical numbering system is based upon the number of atoms in the hydrogen bonded rings, with different configurations resulting in a left or right handed helix. NMR techniques and crystallographic structures have been used to confirm the successful folding properties of conformationally restricted ACHC within a β-peptide 14 helix (Figure 10).[119]

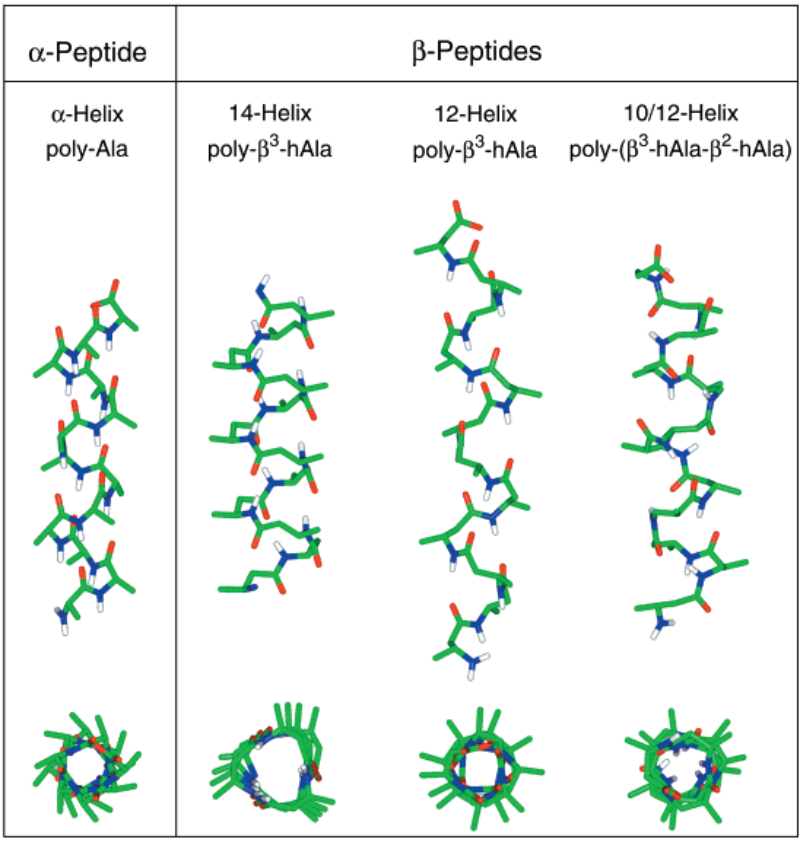


Figure 10- Structure of α and β helices with carbon atoms in green, nitrogen atoms in blue and oxygen atoms in red, with hydrogens omitted for clarity[119]

Such β-peptides are being developed as foldamers with biomedical applications such as antimicrobial activity or protein surface mimicry, after having initially demonstrated promising biological activity.[111] This has significant implications in the drug discovery process as these foldamers could have great potential as drugs that inhibit protein-protein interactions (PPI's) that are related to disease. For example, one recent success involves the synthesis of α/β-oligomers which can mimic both the structure and function of an α-helical segment of the HIV membrane protein gp41, and as a result

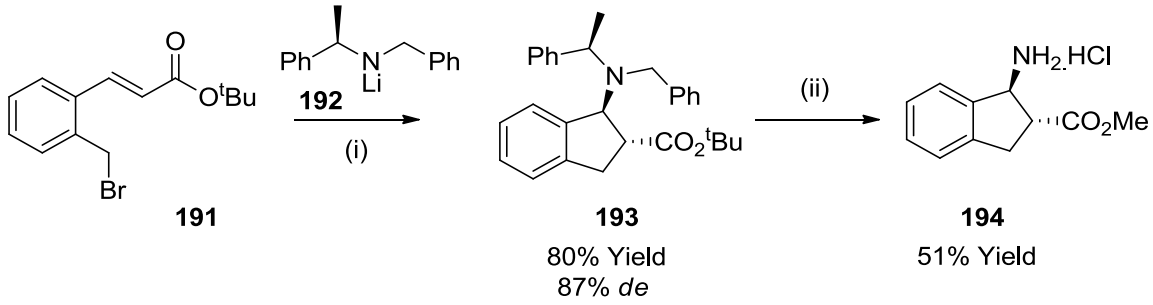
these foldamers have been shown to exhibit potent antiviral activity in HIV anti-infectivity assays.[120]

The success of foldamer research relies on the wide availability of chiral monomers for the generation of specific conformations. As such, the development of methodology for the efficient asymmetric synthesis of cyclic β-amino acid monomers is essential to allow further exploration of secondary and tertiary structures.

2.3 Background - Previous Benzocispentacin Syntheses

There are several reports of different synthetic methods for the asymmetric synthesis of the cyclic β-amino acids shown in Scheme 64. These 1-aminoindane-2-carboxylic acid derived β-amino acids are more commonly referred to as benzocispentacin, which have not only been used for the synthesis of receptor agonists[121] but have also been used for β-peptide synthesis.[122]

Over a decade ago, the asymmetric synthesis of methyl (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-indene-2-carboxylate **193** was achieved by the tandem conjugate addition of a chiral lithium amide **192** equivalent to α,β-unsaturated ester **191**, followed by a subsequent intramolecular electrophilic trap of the intermediate ester enolate.[123] The protected *trans* β-amino ester **193** was obtained in 80% yield and 87% *de* and was successfully deprotected to afford the parent β-amino ester **194** (Scheme 65).[123]



191 **193** **194**

80% Yield
87% *de*

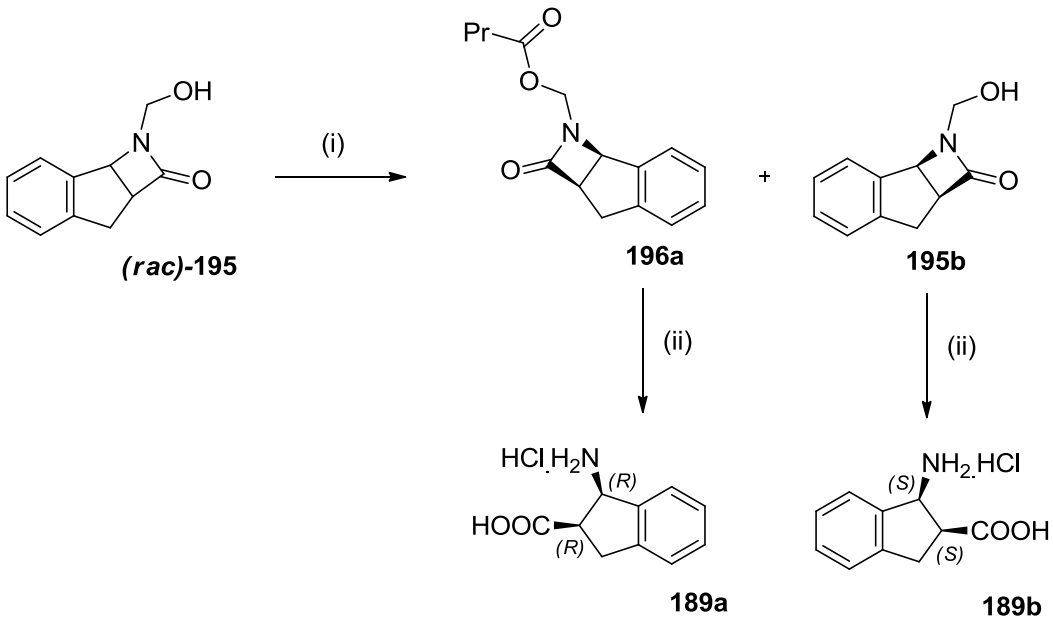
51% Yield

Reagents & Conditions: (i) THF, -78 °C; (ii) a) MeOH, HCl; b) $Pd(OH)_2$, NH_4HCO_2, MeOH, HCl

Scheme 65- Synthesis of bicyclic *trans* β-amino ester 194[123]

In 2000, both enantiomers of benzocispentacin were obtained by enzymatic resolution of the corresponding *N*-hydroxymethylated β-lactams **195**.[124] The kinetic resolution methodology used a lipase catalysed esterification step to generate enantiopure

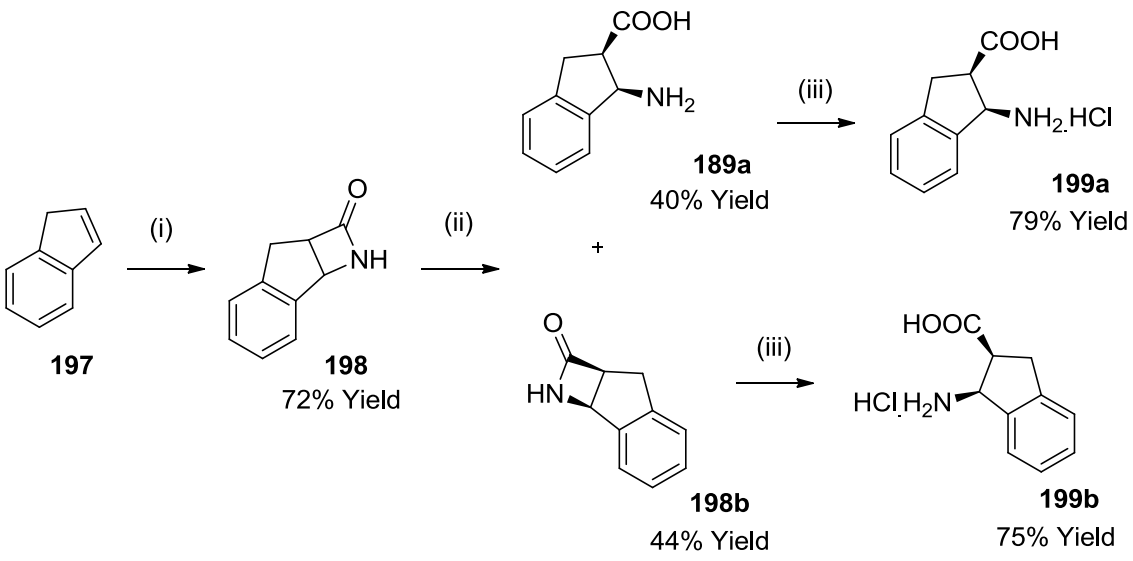
tricyclic β-lactams **189a** and **189b** as shown in Scheme 66.[125] The β-lactams **195b** and **196a** were obtained in 42% and 44% yields respectively and were easily hydrolysed and deprotected to afford the corresponding β-amino acids.[124]



Reagents & Conditions: (i) Lipase PS, vinyl butyrate in acetone, RT, 4hrs; (ii) HCl (aq)

Scheme 66- Lipase PS catalysed β-lactam opening[124]

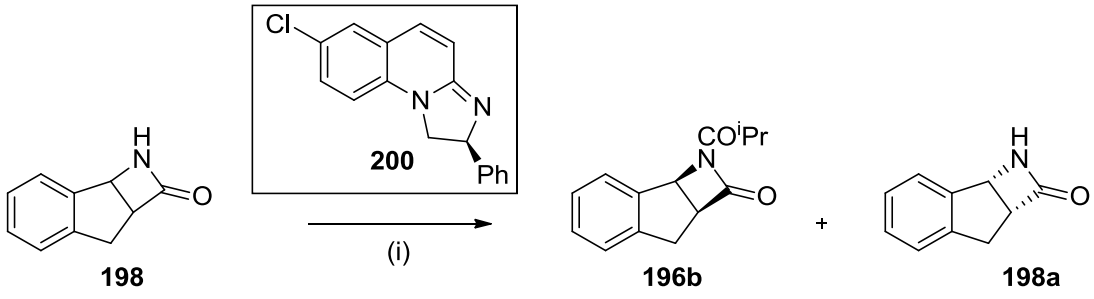
Further to this, an improved enzymatic kinetic resolution method based on hydrolysis of NH-β-lactam **198** was reported,[126] that offered a more direct route to benzocispentacin and its six and seven membered ring analogues. Lipolase catalysed enantioselective ring opening of 3,4-benzo-6-azabicyclo-[3.2.0]heptan-7-one provided access to both the (1*R*,2*R*)-β-amino acid **189a** and the (1*S*,8*S*)-β-lactam **198b**. The (*R,R)*- β-amino acid **189a** was easily isolated with good yields of 40% and an *ee* of greater than 96%. Using aqueous HCl the remaining β-lactam **198b** was ring opened to afford **199b** in a 75% yield and an enantiomeric excess of 99%, resulting in a highly efficient enzymatic synthesis of benzocispentacin (Scheme 67).[126] More recently this synthesis has been shown to be successful using a solvent-free method using 0.5 equivalents of water as the only reagent.[127]



Reagents & Conditions: (i) a) Chlorosulfonyl isocyanate; b) Na_2SO_3; (ii) H_2O, Lipolase, 60 °C; (iii) 18% HCl

Scheme 67- Synthesis of enantiopure benzocispentacin[126]

Although both these methods allow access to both benzocispentacin enantiomers, there are several drawbacks with this enzymatic based methodology. For example, if a specific enantiomer is required then a maximum yield of only 50% can be obtained. Further to this, enzymes are very temperature, pH and substrate specific which can be problematic when preparing a series of structural analogues. More recently, a non-enzymatic kinetic resolution protocol has been developed that involves the use of the amidine, (*S*)-Cl-PIQ **200**, as a nucleophilic catalyst for the *N*-acylation of 4-aryl β-lactams.[128] The β-lactam **198a** gave a moderate 42% conversion, with a relatively low selectivity factor compared to other polycyclic β-lactams in the study (Scheme 68).[128]

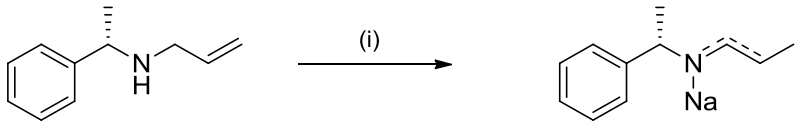


*Reagents & Conditions: (i)10 mol% of **200**, ($^iPrCO)_2O$, $^iPr_2NEt$, tert-amyl alcohol, 0 °C, 30 hrs*

Scheme 68- Kinetic resolution of β-lactams *via* an organocatalytic *N*-acylation strategy

2.4 Background- Intramolecular Enolate-Imine Cyclisation Reactions Generating Multiple Stereocentres

Andrews *et al.* have previously reported the significance of changing alkali metal counterions from lithium to sodium in (*S*)-*N*-(α-methylbenzyl)allylamine complexes.[129] Unlike the stable lithium amide, the respective sodium complex was seen to undergo a 1,3-sigmatropic rearrangement to generate the corresponding 1-aza allyl species **202** (Scheme 69).

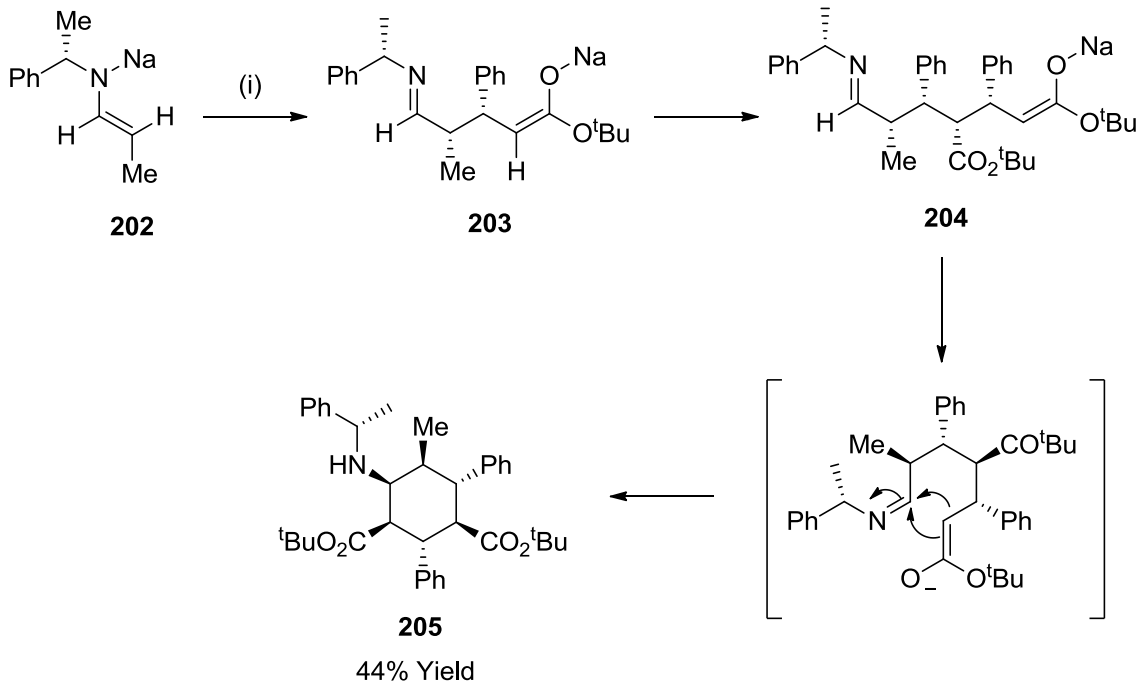


201 **202**

Reagents & Conditions: (i) ^{n}BuNa, TMEDA

Scheme 69- Sodium amide 1,3-sigmatropic rearrangement[130]

Such aza-allyl species were shown to undergo conjugate additions with α,β-unsaturated esters with high stereoselectivity,[131] for the construction of a highly functionalised cyclohexylamine containing six contiguous stereocentres in a one-pot reaction. The reported conjugate addition involves addition of one equivalent of (*E*)-aza-allyl amide **202** to two equivalents of (*E*)-*tert*-butyl cinnamate. The aminocyclohexane **205** was isolated in 44% yield as a single major product,[132] with the absolute configuration of the stereocentres being determined using X-ray crystallography (Scheme 70).



202 **203** **204**

205

44% Yield

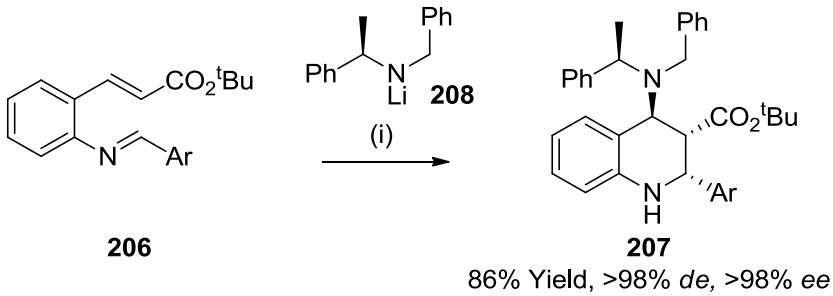
Reagents & Conditions: (i) tert-butyl cinnamate (2.0 equiv.), THF, -78 °C, 12 hrs

Scheme 70- One-pot cascade for the asymmetric synthesis of cyclohexylamine 205[132]

The proposed mechanism suggests a *cis*-selective conjugate addition of the sodium aza-allyl species **202** to the first equivalent of the (*E*)-*tert*-butyl cinnamate generating a (*Z*)-*tert* butyl ester enolate **203** *via* an eight membered cyclic transition state. The enolate then undergoes a *cis* selective Michael addition onto the second equivalent of (*E*)-*tert*-butyl cinnamate to give an (*Z*)-*tert*-butyl ester enolate **204**. In the final step of this reaction cascade a 6-*exo*-trig ring closure reaction of the enolate fragment of **204** on to its imino functionality occurs with high diastereoselectivity,[132] as shown in Scheme 70. The ability to generate six new contiguous stereocentres, all with excellent stereocontrol, based on a single (*S*)-*N*-(α-methylbenzyl)allylamine fragment is remarkable.[132]

More recently there have been further reports of β-amino acid derivatives with multiple contiguous stereocentres having been formed from one-pot reactions.[133] For instance in 2009, Davies *et al.* reported a tandem conjugate addition/cyclisation reaction that generates a cyclic β-amino ester **207** with three contiguous stereocentres as shown in Scheme 71.[134] The conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide

208 results in an enolate that undergoes a subsequent 6-*endo*-trig cyclisation reaction to produce a series of 2-aryl-4-aminotetrahydroquinoline-3-carboxylic acids **207** in 98% *de*.[134]



Reagents & Conditions: (i) THF, -78 °C, 3 hrs

Scheme 71- A tandem conjugate addition/cyclisation reaction[134]

These examples demonstrate the potential for new intramolecular enolate-imine cyclisation protocols to be used for the asymmetric synthesis of cyclic β-amino acids with multiple stereocentres. In light of this, the initial goal of this project was to further explore the final enolate-imine cyclisation step of the cascade reaction shown in Scheme 70, by using simple substrates in the presence of a chiral auxiliary to synthesise a range of chiral cyclic β-amino acids.

2.5 Retrosynthesis of Cyclisation Substrate

In order to adapt the intramolecular enolate-imine methodology (Scheme 70) to produce cyclic β-amino acids, the first aim was to devise a retrosynthetic route that would enable the desired cyclisation substrates to be prepared (Figure 11).

Therefore, based on simplicity of synthesis, it was decided that the first pathway to be explored would involve using a chiral amine auxiliary for stereocontrol. The starting material of 2-bromobenzaldehyde **209** would have a C3-saturated ester side chain attached to the *ortho* position of the aryl ring and then the aldehyde functionality would be converted into an imine using the chiral amine. An enolate-imine cyclisation reaction could then be carried out in order to generate the desired cyclic β-amino ester, which could be deprotected as required.

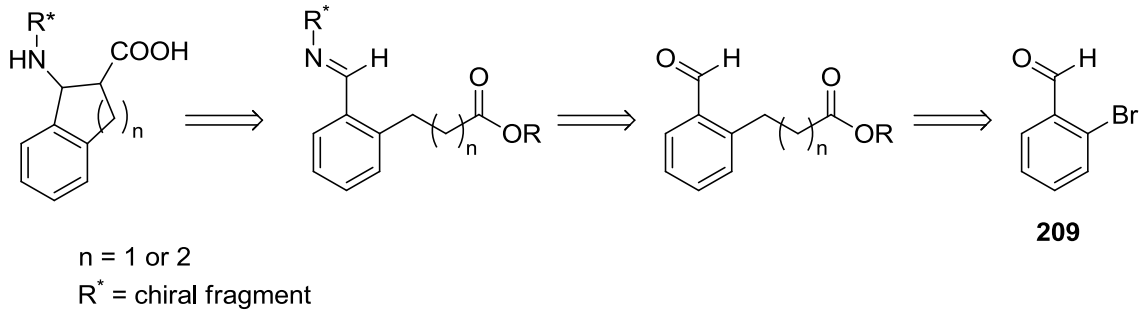


Figure 11 - Retrosynthetic analysis of a cyclic β-amino acid

With this in hand, the next step was to devise an appropriate methodology in order to synthesise the required chiral ω-imino ester.

2.6 Synthesis of (*S*)-*N*-(α-methyl-*p*-methoxybenzyl)-ω-imino-esters

The imino-ester in Figure 12 was chosen as an initial substrate to carry out investigations into using the enolate-imine cyclisation methodology for the synthesis of cyclic β-amino esters.

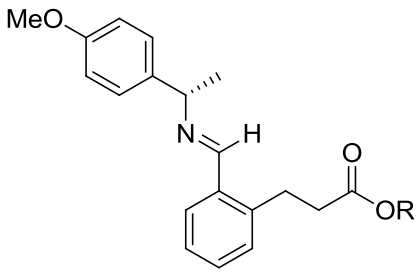
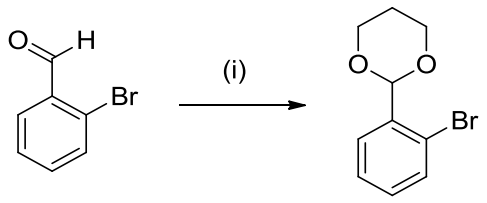


Figure 12- Target substrate for enolate-imine cyclisation

This target structure had many benefits as a starting point for the development of a stereoselective enolate-imine cyclisation reaction. Firstly, the benzylic (*E*)-imine is configurationally stable, while there is no potential for competing enamine formation. Secondly, the aryl ring should predispose the conformation of the derived enolate towards 5-*exo*-trig cyclisation on to its imino functionality. Finally, (*S*)-α-methyl-*p*-methoxybenzylamine was chosen as the chiral auxiliary over the cheaper (*S*)-α-

methylbenzylamine, because it could be subsequently removed under either hydrogenolytic (Pd/C, H_2), or oxidative (CAN, MeCN/H_2O) conditions.

To obtain the target substrate using the retrosynthesis shown in Figure 11, the first step of our synthesis required protection of the aldehyde functionality of 2-bromobenzaldehyde **209** to afford its corresponding acetonide **210**. This was achieved *via* treatment of **209** with propan-1,3-diol, in the presence of a catalytic amount of *p*-toluenesulfonic acid at reflux for three hours (Scheme 72). A Dean-Stark trap was used to remove the water produced and drive the equilibrium of the reaction towards acetonide formation. The resultant 2-(2-bromophenyl)-1,3-dioxane **210** was obtained as a white crystalline solid in 80% yield.



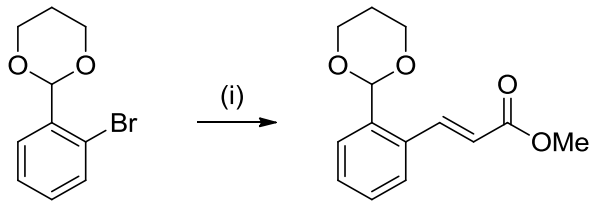
209 **210**

80% Yield

Reagents & Conditions: (i) Propan-1,3-diol, pTSA (cat.), Toluene, reflux, 3 hrs

Scheme 72- Synthesis of 2-(2-bromophenyl)-1,3-dioxane

The Mizoroki-Heck reaction is an efficient method that couples an aromatic halide and an electron deficient alkene using a palladium catalyst and a strong base.[135-136] Therefore, treatment of acetonide **210** and methyl acrylate with a catalytic amount of palladium(II)acetate and the ligand tri(*o*-tolyl)phosphine gave the α,β-unsaturated ester **211** in 84% yield (Scheme 73).[137]



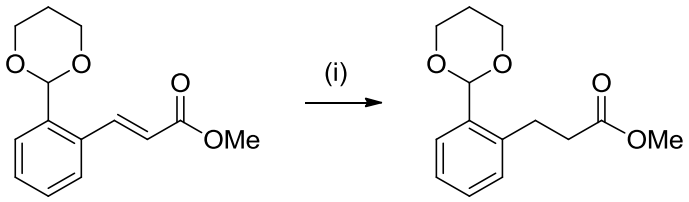
210 **211**

84% Yield

Reagents & Conditions: (i) Methyl acrylate, $Pd(OAc)_2$, $P(o\text{-}Tol)_3$, DIPEA, MeCN, 12 hrs

Scheme 73- Synthesis of methyl 3-(2-(1,3-dioxan-2-yl)phenyl)acrylate

The next stage was removal of the alkene functionality of α,β-unsaturated ester **211**. Initially, a hydrogenation reaction using palladium on carbon was attempted on the methyl α,β-unsaturated ester **211** at atmospheric pressure, which gave only recovered starting material. Subsequently the hydrogen pressure was increased to 4 atm and left for seven hours, which afforded the desired saturated ester **212** in 82% yield (Scheme 74).

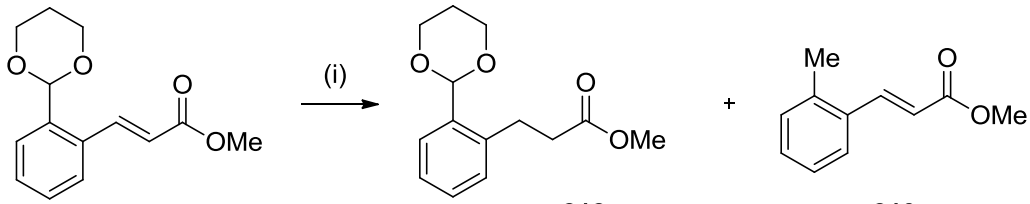


211 **212**
82% Yield

Reagents & Conditions: (i) H_2 (4 atm), Pd/C, MeOH, 7hrs

Scheme 74- Synthesis of methyl 3-(2-(1,3-dioxan-2-yl)phenyl)propanoate acid by hydrogenation

This hydrogenation reaction was successful on a small scale using 300 mg of acetonide **211** or less. However, when the reaction was scaled up it became apparent that the yield of ester **212** decreased dramatically, with most reactions affording significant amounts of starting material. To counteract this, both the pressure and length of time of the hydrogenation reaction were increased, including leaving the hydrogenation reaction for over 24 hours. Unfortunately, this did not increase the proportion of the desired ester **212** instead, affording competing products such as **213** arising from hydrogenolytic cleavage of the acetal functionality (Scheme 75).

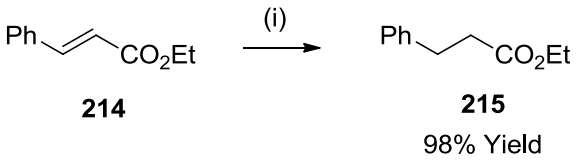


211 **212** **213**
1 : 1

Reagents & Conditions: (i) H_2 (4 atm), Pd/C, MeOH, 24hrs

Scheme 75- Palladium catalysed hydrogenolytic cleavage of acetonide

This resulted in an alternative and improved method for alkene reduction being investigated. In 2008, a chemoselective reaction was reported involving conjugate reduction of α,β-unsaturated ester **214** using sodium borohydride and cobalt(II)chloride in ethanol. Jagdale *et al.*[138] described chemoselective reduction of the alkene functionality of ester **214**, which they used as part of their practical synthesis of (*R*)-tolterodine (Scheme 76).



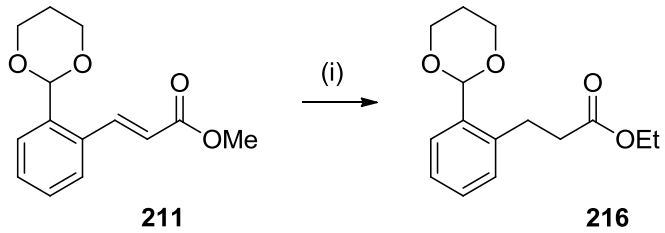
214 **215**

98% Yield

Reagents & Conditions: (i) $NaBH_4$, $CoCl_2 \cdot 6H_2O$, EtOH, 10hrs

Scheme 76- Chemoselective conjugate reduction of ethyl cinnamate[138]

These conditions were successfully applied to the conjugate reduction of methyl ester **211**, which gave its corresponding ethyl ester **216**, arising from alkene reduction as well as an unexpected Lewis acid catalysed transesterification reaction with the solvent ethanol (Scheme 77).

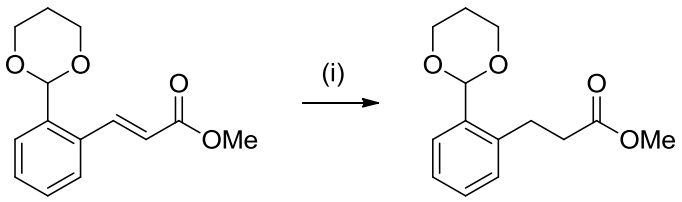


211 **216**

Reagents & Conditions: (i) $NaBH_4$, $CoCl_2 \cdot 6H_2O$, EtOH

Scheme 77- Chemoselective reduction of ester 211 using cobalt(II)chloride

To confirm this, the reduction reaction was repeated using methanol as solvent with all other conditions remaining constant, which produced the desired saturated methyl ester **212** in 70% yield after 72 hours (Scheme 78).



211 **212**

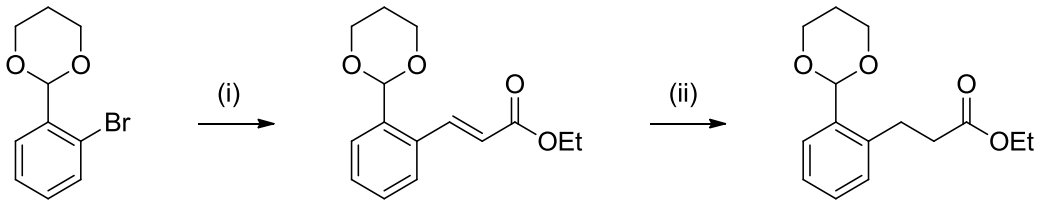
70% Yield

Reagents & Conditions: (i) $NaBH_4$, $CoCl_2 \cdot 6H_2O$, MeOH

Scheme 78- Chemoselective reduction of ester 211 using cobalt(II)chloride in methanol

In 1982, Heinzman *et al*. proposed that cobalt boride is formed in sodium borohydride cobaltous chloride reduction reactions, which subsequently coordinates to the alkene and as such catalyses a conjugate reduction reaction.[139] This method is much milder than using H_2 gas under pressure as the $NaBH_4$ provides a source of H_2 *via* decomposition over cobalt boride while possibly following a similar mechanism to the Luche reduction.

Therefore, due to the occurrence of the trans-esterification process and the availability of ethyl acrylate, it was decided to carry out a chemoselective conjugate reduction on the ethyl α,β-unsaturated ester **217**, yielding the saturated ethyl ester in 81% yield (Scheme 79).



210 **217** **216**

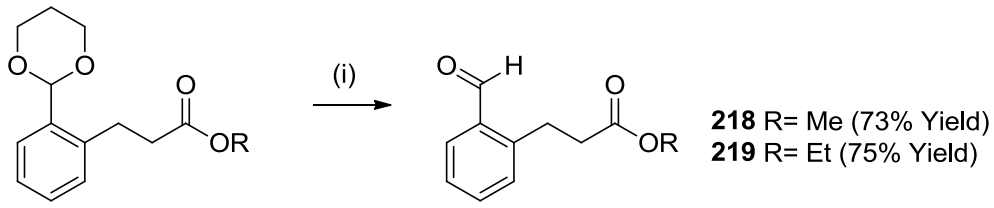
96% Yield 81% Yield

Reagents & Conditions: (i) Ethyl acrylate, $Pd(OAc)_2$, $P(O\text{-}Tol)_3$, DIPEA, MeCN; (ii) $NaBH_4$, $CoCl_2 \cdot 6H_2O$, MeOH

Scheme 79- Synthesis of ethyl 3-(2-(1,3-dioxan-2-yl)phenyl)acrylate 217

Following the success in obtaining samples of both methyl 3-(2-formylphenyl)propanoate **212** and ethyl 3-(2-formylphenyl)propanoate **216**, it was now necessary to develop conditions that would allow deprotection of their acetal functionalities. After screening a range of deprotection conditions, it was found that

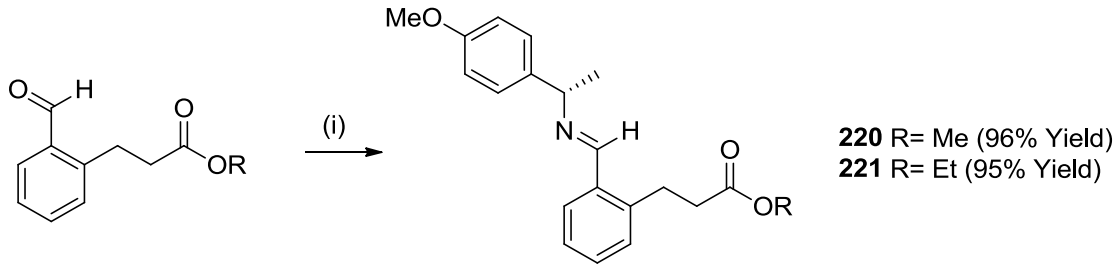
addition of acetic acid and water for 12 hours resulted in the acetal protecting group being smoothly removed to afford the desired aldehydes **218** and **219** (Scheme 80).



Reagents & Conditions: (i) AcOH, H_2O, 12 hrs

Scheme 80- Hydrolysis of acetals 212 and 216

The desired imines **220** and **221** were then prepared in essentially quantitative yield *via* addition of (*S*)-α-methyl-*p*-methoxybenzylamine to aldehydes **218** and **219** respectively. The equilibrium of imine formation was driven to completion by the use of magnesium sulphate to remove the water produced in the reaction (Scheme 81).



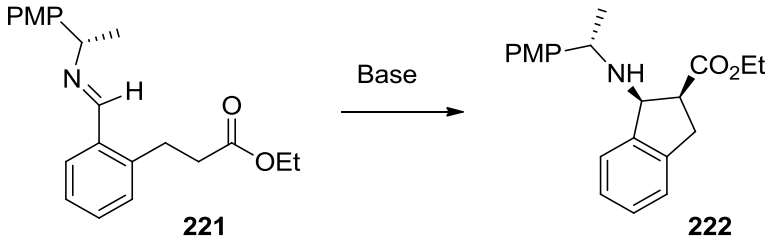
Reagents & Conditions: (i) (S)-α-Methyl-p-methoxybenzylamine, $MgSO_4$, DCM, 5hrs

Scheme 81- Synthesis of chiral imino-ω-esters 220 & 221

The chiral imines **220** and **221** were generated in sufficient quantity to be used as substrates to investigate our proposed 5-*exo*-trig cyclisation methodology for the synthesis of β-amino acids.

2.7 Initial Attempts at Developing an Intramolecular Enolate-Imine Cyclisation Reaction

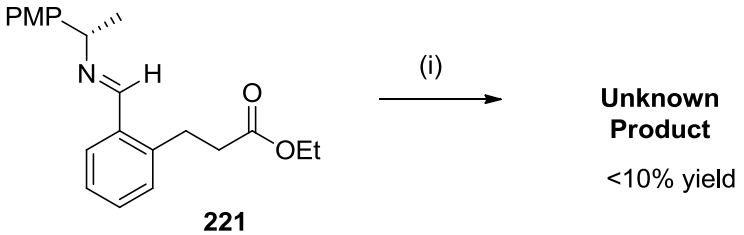
With the desired chiral imino ester in hand (Figure 12), the next step was to generate its enolate in order to initiate a 5-*exo*-trig cyclisation reaction. At the outset, LiHMDS was chosen as a strong, bulky, non-nucleophilic base, which based on the precedent of Andrews *et al.*[132] was predicted to afford an enolate that would cyclise to produce a *cis*-β-amino ester such as **222** (Scheme 82).



221 **222**

Scheme 82- Proposed cyclisation reaction

Initially, the generation of the enolate of chiral-ω-imino-esters, (*S*)-ethyl 3-(2-(((1-(4-methoxyphenyl)ethyl)imino)methyl)phenyl)propanoate **221**, was attempted using 1.1 equivalents of LiHMDS as a base over an eight hour period at -78 °C, in keeping with the original conditions developed for the one-pot synthesis (Scheme 70).[132] Unfortunately, only starting material was recovered, so the reaction was repeated, but this time it was allowed to warm from -78 °C to room temperature. The crude reaction product still contained largely starting material, but small amounts (<10%) of major and minor diastereomeric products were present. ^{1}H NMR analysis of the crude product reaction revealed that these diastereomers were not the cyclic β-amino ester products as expected (Scheme 83).

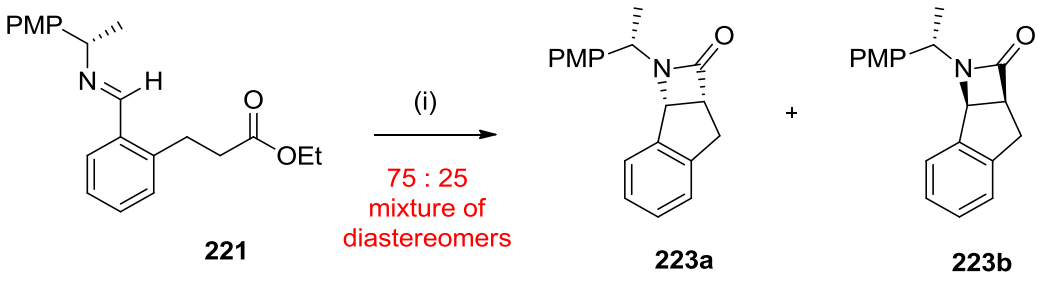


221

Reagents & Conditions: (i) LiHMDS (1.1 equiv.), THF, -78 °C to rt, 8 hrs

Scheme 83- Initial cyclisation reaction using LiHMDS as a base

An appropriate solvent system was established for the separation of the two diastereomers by flash column chromatography, which enabled the major diastereomer to be isolated. Once isolated, the ^{1}H NMR spectrum of the major diastereomer suggested that the cyclisation had occurred as envisaged, however an absence of peaks for an ethyl ester functionality suggested the potential formation of a cyclic β-lactam. Inspection of the IR data did not show the expected broad absorption between 2500-3300 cm^{-1} for a carboxylic acid group. A carbonyl absorption at 1731 cm^{-1} suggested either an ester (1735 cm^{-1}) or possibly a β-lactam (1745 cm^{-1}).[140] When examining the ^{13}C spectrum of the major diastereomer a carbonyl peak was observed at 170 ppm, which was slightly lower than expected for a β-amino acid (usually around 180 ppm). However, such values correlate well with those previously reported for the carbonyl of a strained β-lactam ring (between 167 ppm and 173 ppm).[141] Finally, the high resolution mass spectrometry data revealed a clean and well defined m/z value of 294.14, consistent with the formation of a β-lactam **223**. Therefore based on the data in hand it was proposed that the products formed were a set of diastereomers of the β-lactam as shown in Scheme 84.



221 **223a** **223b**

Reagents & Conditions: (i) LiHMDS (1.1 equiv.), THF, -78 °C to rt, 8 hrs

Scheme 84- Identifcation of unexpected β-lactam products

The major diastereomer has a diagnostic doublet observed at 1.44 ppm and a quartet at 5.00 ppm whilset the minor diastereomer has a diagnostic doublet observed at 1.71 ppm and a quartet at 4.48 ppm. Subsequently a COSY spectrum (Figure 13) of the major diastereomer was obtained, which helped confirm the structure of the major β-lactam diastereomer.

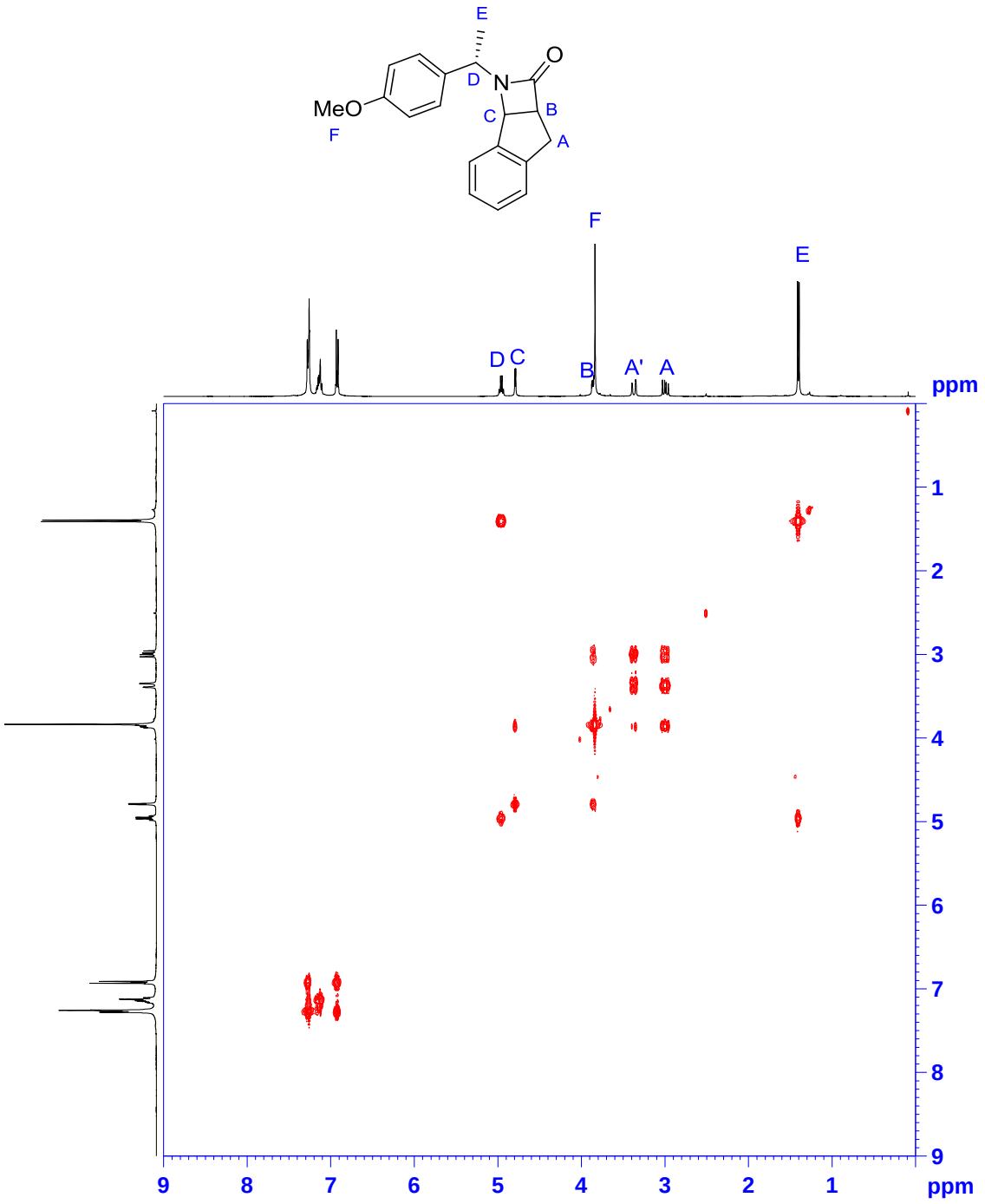


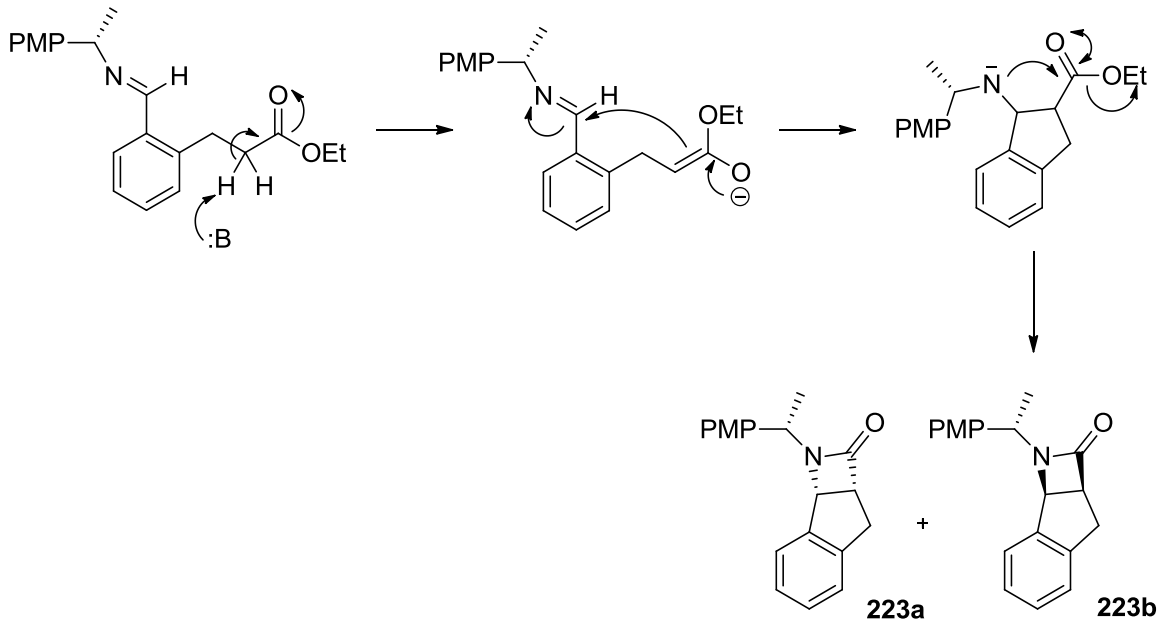
Figure 13- COSY spectrum of β-lactam 223

The COSY spectrum reveals that proton B couples to protons A, A' and C, with a coupling constant of $J_{(BC)}$= 4.5 Hz, which is consistent with that expected for a β-lactam ring system. The bridgehead protons B (δ3.87 ppm) and C (δ4.30 ppm) resonate at a lower field than would be expected for a β-amino acid product. In conjunction with all

the other analytical data it was therefore concluded that the product formed was a tricyclic β-lactam.

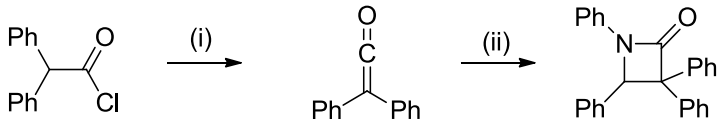
2.8 Mechanism of β-Lactam Formation

There are two possible mechanisms by which β-lactam formation could have occurred. The first proposed mechanism (in its simplistic form) is the formation of an (*E*)-enolate that subsequently attacks the imine fragment in a 5-*exo*-trig manner, resulting in the generation of a highly nucleophilic aza-anion. Consequently, the nucleophilic aza-anion substituent then undergoes a 4-*exo*-trig ring closing reaction to form the respective β-lactams **223a** and **223b** (Scheme 85).



Scheme 85- Enolate mechanism for β-lactam formation

An alternative mechanism could be proposed based upon a Staudinger ketene cycloaddition pathway. This reaction manifold was first reported in 1907, when a [2+2] cycloaddition was employed to produce the first synthetic β-lactam **7** (Scheme 86).[6]

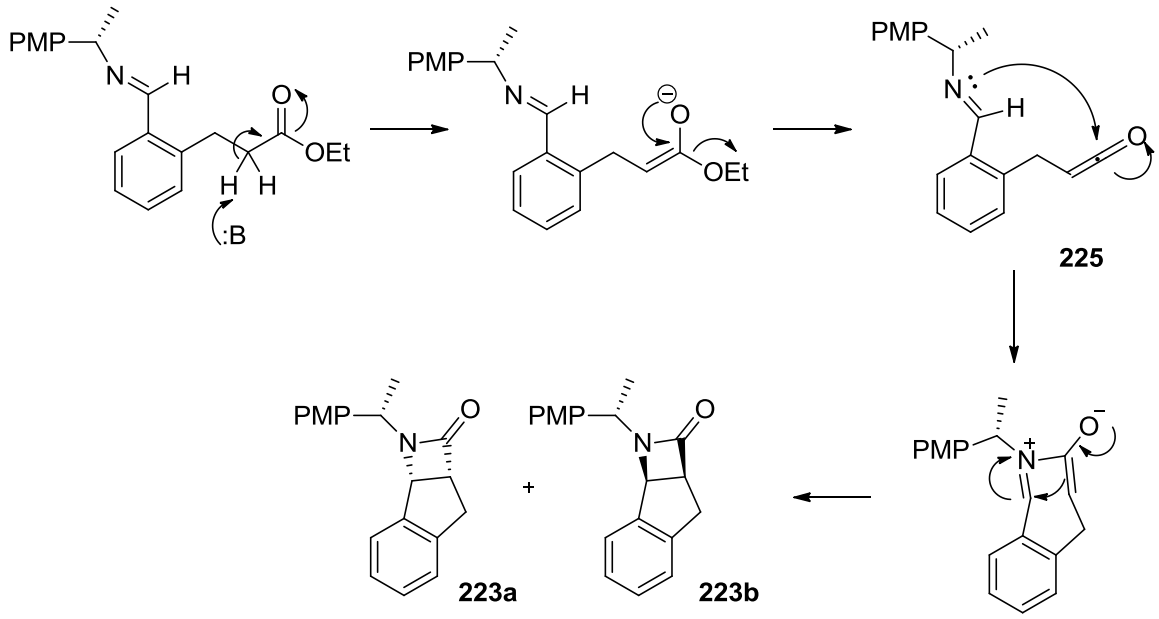


224 **5** **7**

Reagents & Conditions: (i) NEt_3 (ii) N-benzylideneaniline

Scheme 86- Staudinger ketene cycloaddition for the synthesis of β-lactams

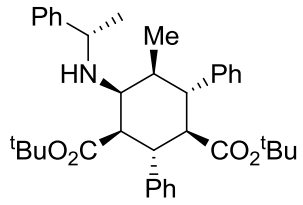
Therefore, an alternative mechanism for β-lactam **223** would require formation of a ketene intermediate **225**. Subsequent nucleophilic attack of the imine lone pair onto the carbonyl of the ketene would then afford a zwitterionic intermediate, whose enolate fragment would then undergo ring closure onto the iminium species to afford the β-lactams **223a** and **223b** (Scheme 87).



Scheme 87- Alternative ketene mechanism for β-lactam formation

A review of the literature reveals that while there are numerous examples of Staudinger cycloaddition reaction using more reactive acid chlorides,[142] there is no such precedent reported for less reactive ester groups. Bearing this lack of precedent in mind, it was concluded that β-lactam formation was proceeding *via* a stepwise enolate-imine cyclisation mechanism. Furthermore, it should be noted that a β-amino ester product

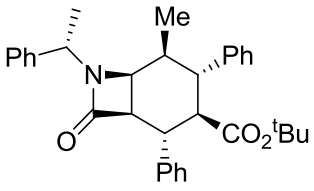
205 was isolated from Andrew *et al.*'s original cyclisation reaction (Figure 14), which is not consistent with a ketene based mechanism operating in these reactions. Therefore, in this case, we suggest that an enolate-imine cyclisation reaction occurs to afford a β-amino ester aza-anion, which is less likely to ring close to afford a β–lactam because of the presence of its bulky *t*-butyl ester.



205

Figure 14- Cyclohexylamine 205 formed from original enolate-imine cyclisation reaction[132]

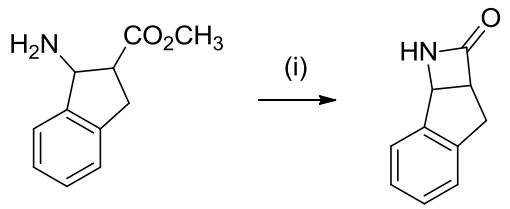
Indeed, further reinvestigation of this cyclisation reaction has recently revealed the presence of a small amount of bicyclic β-lactam **226** present in the crude reaction product of this cyclisation reaction (Figure 15).



226

Figure 15- Minor bicyclic β-lactam 226 product observed from original cyclisation reaction[143]

The 4-*exo*-trig cyclisation of metalated β-amino esters to afford β-lactams is not entirely unexpected, with a review of the literature revealing good precedent for cyclisation. For example in 1974, it was reported that the treatment of (*rac*)-β-amino-ester **227** with MeMgI gave racemic β-lactam **228**, albeit in only 12% yield (Scheme 88).[144]

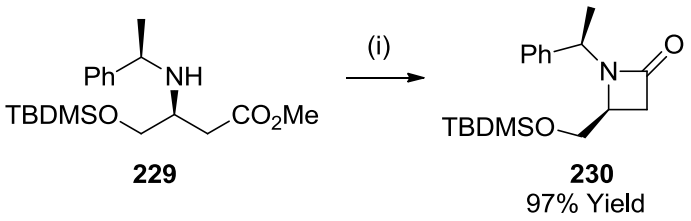


227 **228**
12% Yield

Reagents & Conditions: (i) MeMgI, Et_2O, 0 °C, 2 hrs.

Scheme 88- Synthesis of 7-ketobenzo[c]*cis*-6-azabicyclo[3.2.0]heptanes 228[144]

In 2007, Davies *et al.* showed that magnesium amides cyclise to afford chiral β-lactams in a similar manner.[145] It has also been shown that it is possible to generate β-lactams *via* the action of titanium halides[146] and tin(II)amides[147] on related precursors; in good yields (Scheme 89).

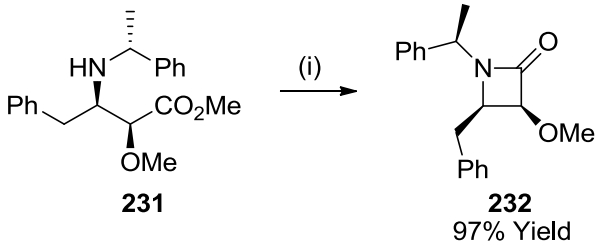


229 **230**
97% Yield

Reagents & Conditions: (i) MeMgBr, Et_2O, 0 °C

Scheme 89- Synthesis of a β-lactam using MeMgBr to facilitate cyclisation[145]

More directly related, Ha *et al*. have shown that treatment of β-amino ester **231** with LiHMDS in THF at -78°C, resulted in cyclisation to afford β-lactam **232** in 97% yield (Scheme 90).[148] In conclusion, this evidence suggests that formation of β-lactam **223** occurs *via* an enolate-imine cyclisation mechanism.



231 **232**
97% Yield

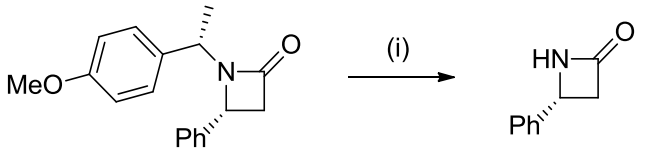
Reagents & Conditions: (i) LiHMDS, THF, -78 °C to 0 °C, 2hrs

Scheme 90- Lactamisation reaction using LiHMDS as a base to induce cyclisation[148]

2.9 Determination of the Configuration of β-Lactam 223

In light of the discovery of this β-lactam forming reaction and the ability to isolate the major diastereomer, the next step was to confirm the stereochemistry of the β-lactam **223**.

As the protected tricyclic β-lactam **223** has been reported previously,[126] it was decided to deprotect the major diastereomer **223** and use the sign of the specific rotation to assign its configuration. Davies *et al.* have previously shown that the treatment of β-lactam **233** with ceric ammonium nitrate (CAN) results in oxidative deprotection to afford the β-lactam **234** (Scheme 91).[149]

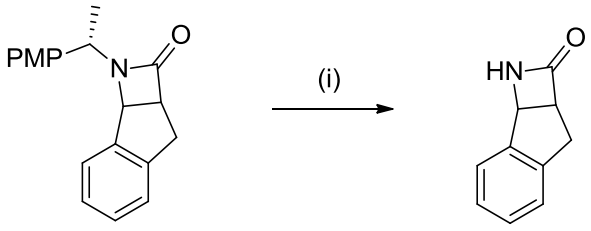


233 **234**
68% Yield

Reagents & Conditions: (i) CAN (3.0 equiv.), MeCN-H_2O (5:1), rt, 16 hrs.

Scheme 91- CAN deprotection reaction of β-lactam 233[149]

With an appropriate deprotection precedent in hand, the next step was to apply this oxidative cleavage methodology to the unknown major diasteromer obtained from the initial cyclisation reaction (Scheme 84). This deprotection strategy was successfully applied to *N*-aryl-β-lactam **223** yielding the free NH-β-lactam **198** in 76% yield.



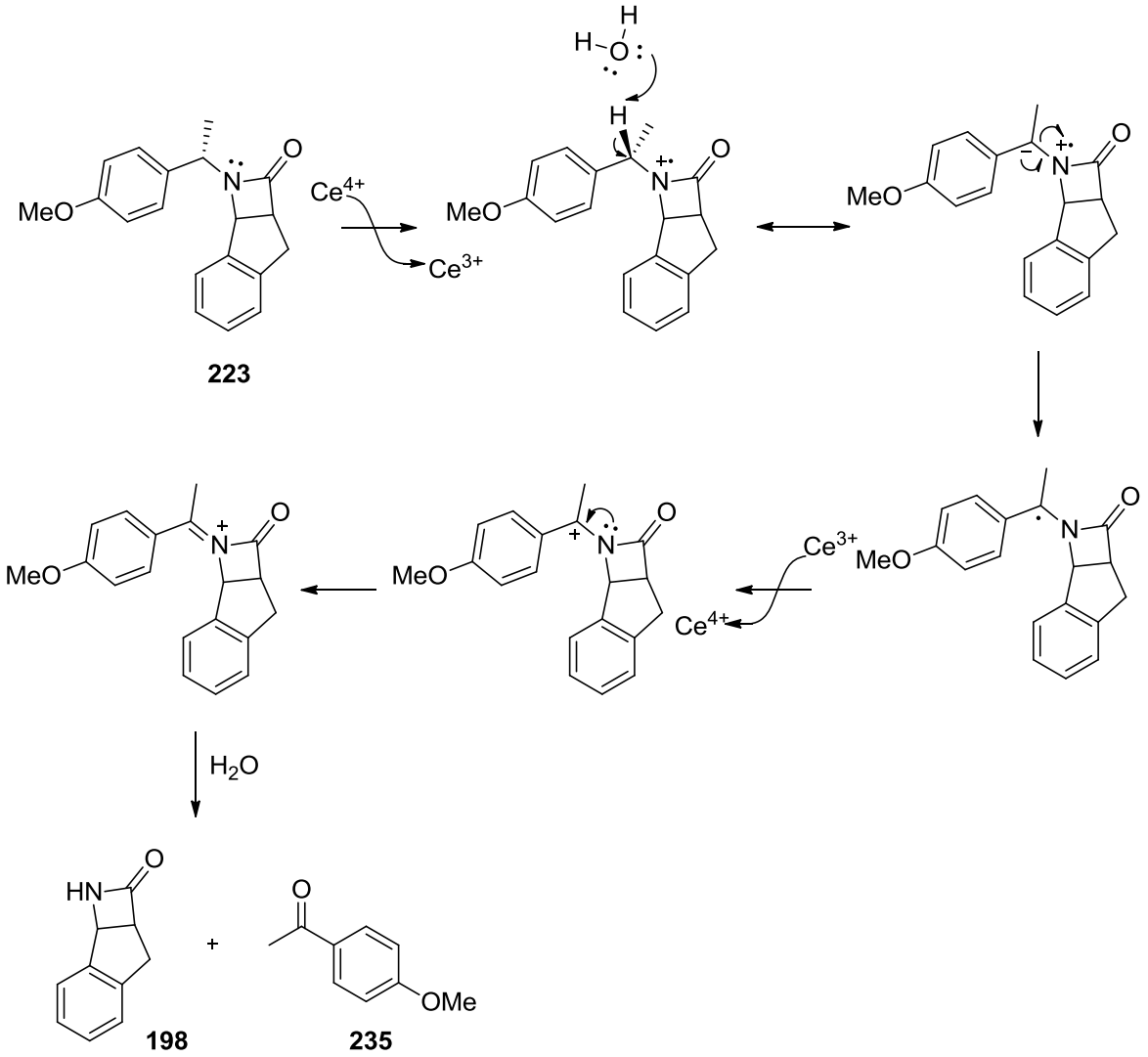
unknown
major diasteroemer
223

198
76% Yield

Reagents & Conditions: (i) CAN (3.0 equiv), MeCN-H_2O (5:1), rt, 16 hrs

Scheme 92- Deprotection of unknown β-lactam diastereomer 223 using CAN

The free radical mechanism for the deprotection of tricyclic β-lactam **223** is shown in Scheme 93.



Scheme 93- Mechanism of CAN mediated deprotection reaction of β-lactam 223

Once purified, the β-lactam **198** was characterized and the identification of the major diastereomer confirmed by comparing the negative sign of its specific optical rotation with the positive values previously reported for its (*S*,*S*)-enantiomer.[126] Therefore, the specific rotation of the (*S*,*S*)-β-lactam diastereomer **198a** was measured as +224 which compares with the previously reported value of -214 for the (*R*,*R*)-β-lactam **198b**.[126]

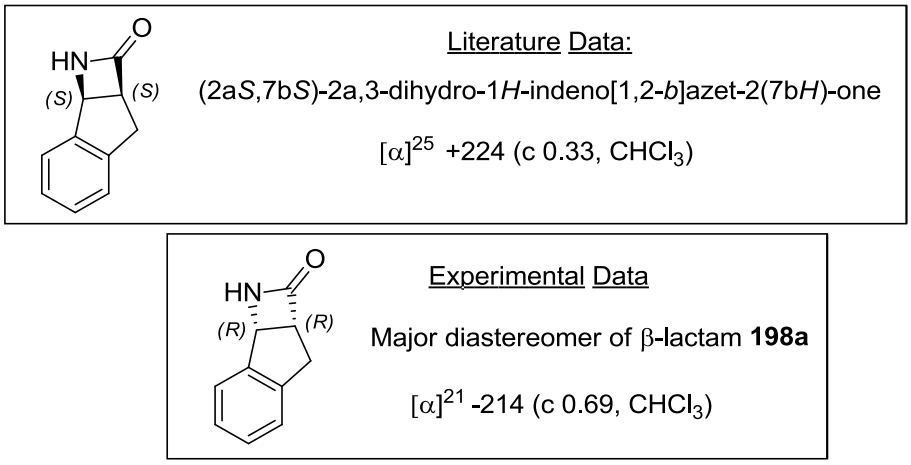
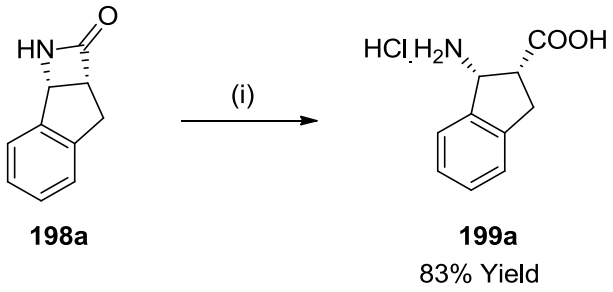


Figure 16- Comparison of specific rotation values of 198 with literature values[126]

This configurational assignment was further confirmed *via* hydrolysis of β-lactam **198a** with aqueous hydrochloric acid to give the known β-amino ester salt hydrochloride salt **199a** (Scheme 94). This β-amino acid salt **199a** was isolated in an 83% yield giving a specific rotation of -2.5 which further correlates with the literature value of -5.7 reported previously for the same enantiomer of this amino acid.[126]



Reagents & Conditions: (i) 18% HCl, reflux, 3hrs

Scheme 94- β-Amino acid synthesis from β-lactam 198a

A successful route had now been devised to prepare one of the model β-amino acid targets; however the 5-*exo*-trig intramolecular enolate-imine cyclisation required optimization to enable the major diastereomer to be isolated in good yield and high *de*.

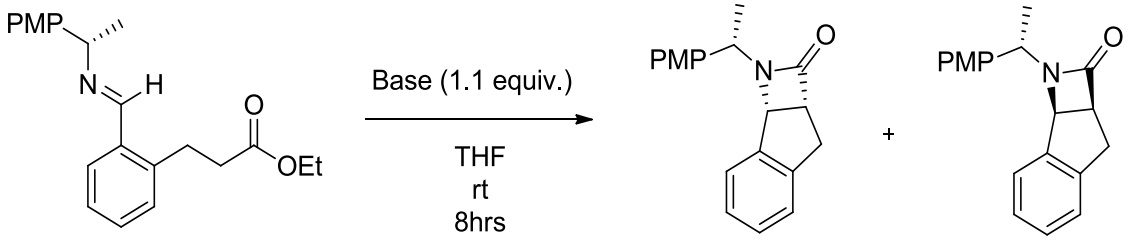
2.10 Optimisation of Enolate-Imine Cyclisation Conditions

Initial attempts at developing the intramolecular enolate-imine reaction (Scheme 84) had shown that the cyclisation reaction proceeded to afford β-lactam **223b**. However, a yield of less than 10% and a diasteromeric excess of 50% were far from ideal and did not represent a useful synthesis of this type of tricylic β-lactam. As such, an attempt to optimize these conditions was undertaken in order to not only improve the diastereoselectivity and yield, but also to provide a better insight into rationalising the stereoselectivity of the cyclisation reaction.

The first variable to be selected was the base used to generate the enolate for cyclisation, with all reactions initially carried out at room temperature. A range of bases varying in pK_a, steric bulk and reactivity were investigated in order to see how readily the enolate-imine cyclisation reaction would occur, and determine which base would provide the best yield and diastereoselectivity.

As can be seen from Table 4 the trend suggested that the enolate-imine cyclisation reaction requires a strong sterically hindered base to proceed with good levels of stereocontrol. Initially, the use of LiHMDS gave a low 37% yield and also a moderate 46% *de* (Table 4, Entry 1). Therefore, the reaction was attempted with the more reactive NaHMDS which showed a marked improvement in the 56% yield and 54% *de* (Table 4, Entry 2). As such, due to the positive correlation between reactivity and improved results, KHMDS was trialed as a base; however this was unsuccessful, with only a small amount of β-lactam being formed in 0% *de* (Table 4, Entry 3). Potassium *tert*-butoxide, a weak base which has previously been reported to synthesise β-lactams in intermolecular enolate-imine condensations,[150] successfully generated β-lactam **223a** but in a low yield of 20% and a poor *de* of 30% (Table 4, Entry 4). Finally, sodium ethoxide, triethylamine and sodium hydride were all trialed but did not yield any β-lactam, with only starting material being recovered (Table 4, Entries 5-7).

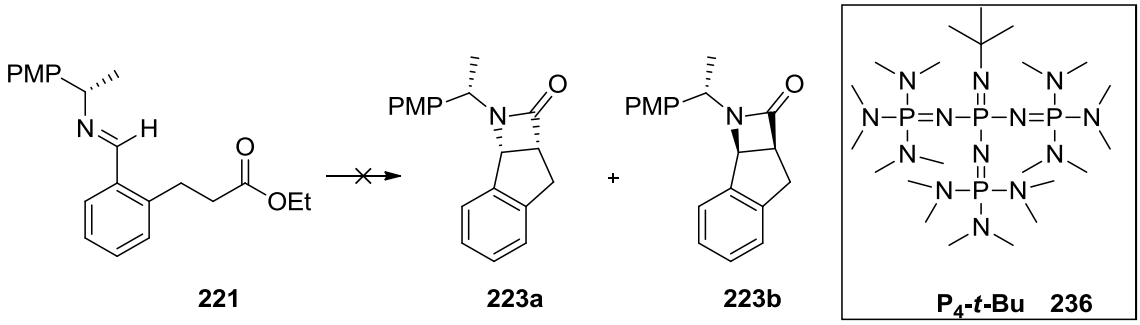
Table 4- Effects of choice of base on yield and diastereoselectivity of β-lactam 223



221 **Major - 223a** **Minor - 223b**

Entry	Base	Yield (%)	*de* (%)
1	LiHMDS	37	46
2	NaHMDS	56	54
3	KHMDS	18	0
4	$(CH_3)_3COK$	20	30
5	NaOEt	0	-
6	Et_3N	0	-
7	NaH	0	-

The non-metallic phosphazene base, also known as a "Schwesinger base",[151] has previously been shown to generate enolates from *iso*propyl acetate,[152] with phosphazene base classed as 'naked' because their counterions are considered to be non-coordinating.[153] Sadly, despite repeated attempts using phosphazene bases under various conditions no β-lactam was ever observed with only starting material being recovered. In light of these results, the base chosen for further reaction optimization steps was NaHMDS (Scheme 95).



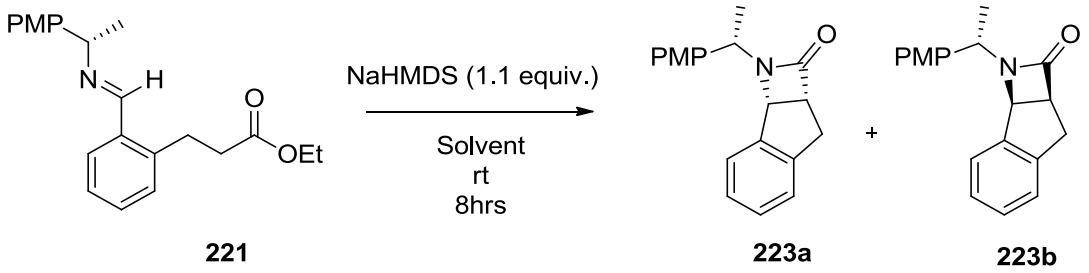
221 223a 223b

Reagents & Conditions: P_4-t-Bu (1M in Hexanes), THF, -78°C to rt, 8 hrs

Scheme 95- β-lactam synthesis using phosphazene base 236

The next variable that was examined was the reaction solvent. Toluene was chosen as a potential alternative as this non-coordinating, non-polar solvent has been successfully shown to improve the stereoselectivity in many enolate generating reactions.[154] In comparison with THF, the cyclisation reaction in toluene gave the β-lactam **223a** in a slightly lower *de* of 48%, but the main effect was on the yield which was considerably reduced to only 14%. Therefore, THF was chosen as the solvent of choice for further reactions (Table 5, Entry 2).

Table 5- Effects of solvent on yield and diastereoselectivity on β-lactam 223



221 223a 223b

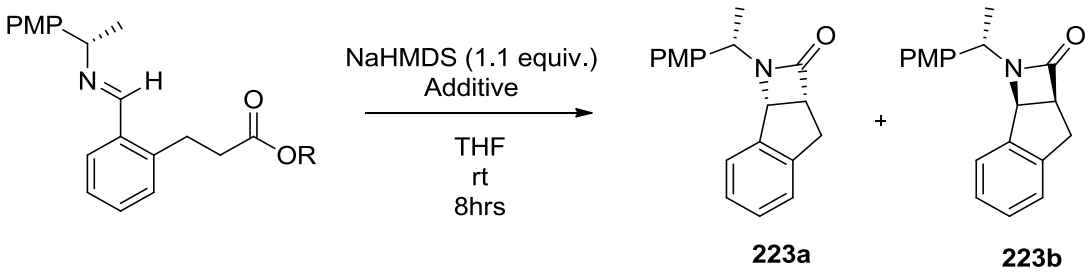
Entry	Solvent	Yield (%)	*de* (%)
1	THF	56	54
2	Toluene	14	48

The next factor to be investigated was to include an additive in the reaction such as a crown ether. Crown ethers are cyclic compounds that contain ether groups which can bind strongly to specific cations depending on their size. In this case, as the base being

used was NaHMDS, the corresponding crown ether required was 15-crown-5. Due to the strong binding of the crown ether to the metal cation, the sodium counterion should not be involved in the transition state, thus generating a highly reactive “naked” enolate that might have a significant impact on the yield and diastereoselectivity.

At the outset, the addition of 15-crown-5 to the reaction was investigated at room temperature. It was found that addition of 15-crown-5 had a significant impact on the *de* increasing it from 54% to 88% (Table 6, Entry 2). The effect of the quantity of base employed were also investigated, both with and without the crown ether. The aim was firstly to prove whether increasing the equivalents of the base (and the crown ether) had an impact on the yield and *de* of the cyclisation reaction, and to subsequently show whether the crown ether was as effective under these conditions.

Table 6- Effects of crown ether additive on yield and diastereoselectivity of β-lactam 223

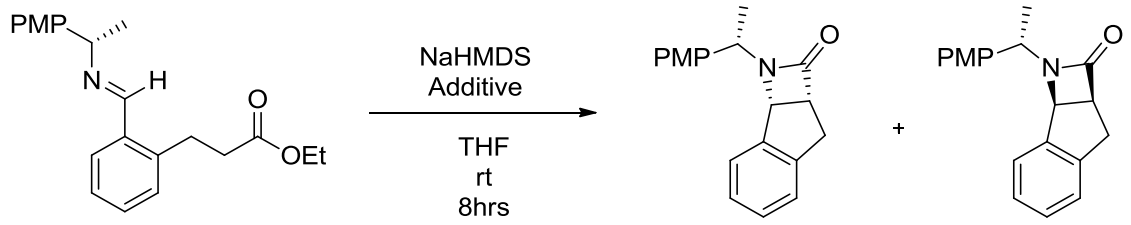


223a **223b**

Entry	R Group	Crown Ether	Yield (%)	*de* (%)
1	OEt	No	56	54
2	OEt	Yes	85	88

As Table 7 shows – the crown ether was as effective at increasing the yield and *de* using 2.0 equivalents of base as it was with 1.1 equivalents. However, the increase in the equivalents of base (and crown ether) showed a negligible difference in yield and the same *de*. Therefore, optimal conditions were established as the used of 1.1 equivalents of base in THF in the presence of a stoichiometric amount of 15-crown-5 that gave an 85% yield of the major diastereomer in 88% *de*.

Table 7 – Effects of equivalents of base on the yield and diastereoselectivity of β-lactam 223



221 **223a** **223b**

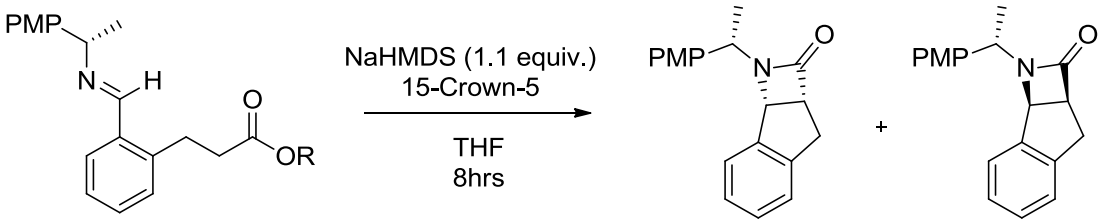
Entry	Equiv of Base	Crown Ether	Yield (%)	*de* (%)
1	1.1	No	56	54
2	2.0	No	66	56
3	1.1	Yes	85	88
4	2.0	Yes	86	88

The final and possibly most important factor to be investigated was temperature. All previous optimization reactions had been carried out at room temperature and so the effect of cooling the reaction was then examined. The temperature at which the enolate is formed could determine whether the thermodynamic or kinetic enolate was formed, as well as improving the facial selectivity of the cyclisation reaction. Therefore, a range of cryogenic temperatures were screened to see what trend between temperature and diastereoselectivity would be observed.

The first step was to perform the cyclisation reaction at -78 °C for 2 hours and gradually allow it to warm to room temperature. Although this gave a poor 5% yield it did produce excellent diastereoselectivity (99% *de*; Table 8, Entry 2) which was not completely unexpected as stereoselectivity is normally improved at cryogenic temperatures. Therefore, in an attempt to improve the yield, but not to compromise the diastereoselectivity, the cyclisation reaction was carried out at -45 °C for 2 hours before warming to room temperature. This gave a very good and much improved yield of 73% while not affecting the diastereoselectivity which remained at 99% *de* (Table 8, Entry 3). The cyclisation was then attempted at 0 °C for 2 hours before warming to room temperature to see if the yield could be increased even further, this gave only a 67%

yield and a drop in *de* to 90% (Table 8, Entry 2). Finally the reaction was carried out at room temperature and these conditions saw a slight drop in the yield but the main drawback was the substantial decrease in the *de* from 99% to 88% *de* (Table 8, Entry 1). These finding suggested that the optimal temperature profile for this enolate-imine cyclisation reaction is to start at -45 °C for 2 hours and allow the reaction to slowly warm to room temperature.

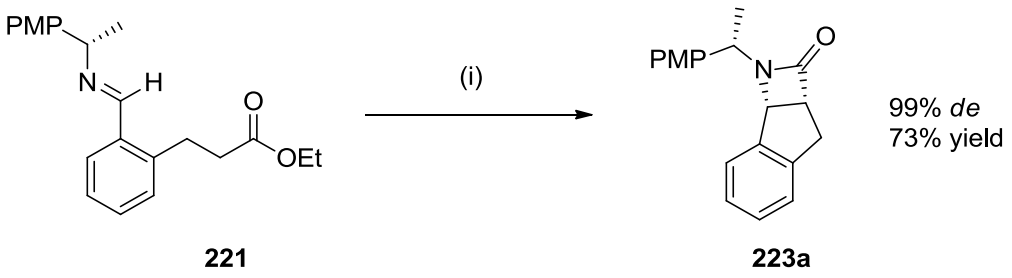
Table 8- Effects of temperature on the yield and diastereoselectivity of β-lactam synthesis



221 **223a** **223b**

Entry	Temp (°C)	Yield (%)	*de* (%)
1	rt	86	88
2	-78 to rt	5	99
3	-45 to rt	73	99
4	0 to rt	67	90

In conclusion, the optimization process had allowed a set of conditions to be identified that enabled the asymmetric synthesis of β-lactam **223a** to be carried out in good yield and with excellent levels of stereocontrol. The most significant modifications included the addition of a crown ether and reducing the temperature of the reaction to -45 °C, which allowed β-lactam **223a** to be formed in an excellent *de* of 99% and a good 73% isolated yield.



221 **223a**

Reagents & Conditions: (i) NaHMDS (2.0 equiv.), 15-crown-5, THF, -45 °C to rt, 8 hrs

Scheme 96- Optimised conditions for β-lactam synthesis

Not only did this generate a suitable methodology for the synthesis of β-lactam **223a**, but also the possibility of using it to generate a range of β-lactam analogues.

2.11 Occurrence of a Minor β-Amino Ester Side Product

Upon further inspection of the ^{1}H NMR spectra of the crude reaction products of some of the enolate-imine cyclisation reactions described in the previous section, there were a few examples where a minor side product was present. This was significant as it could provide further understanding of the mechanism of the enolate-imine cyclisation reaction.

Consequently, it was found that treatment of ester **221** with KHMDS in THF at room temperature resulted in a crude reaction product that was purified by chromatography to afford a small amount of a β-amino ester side product. The ^{1}H NMR spectrum of this side product contained a triplet at 1.24 ppm and a quartet at 4.19 ppm suggesting that the ethyl ester group was still present. Further to this, the presence of multiplets at 3.18 ppm and 3.36 ppm of its bridgehead ring protons indicated that the initial 5-*exo*-trig cyclisation had also taken place. In addition, the high resolution mass spectrometry data reported a clean and well defined m/z value of 340.19, consistent with the presence of a β-amino ester shown in Figure 17.

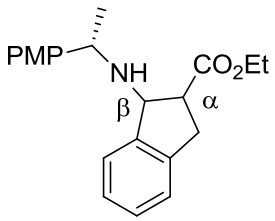
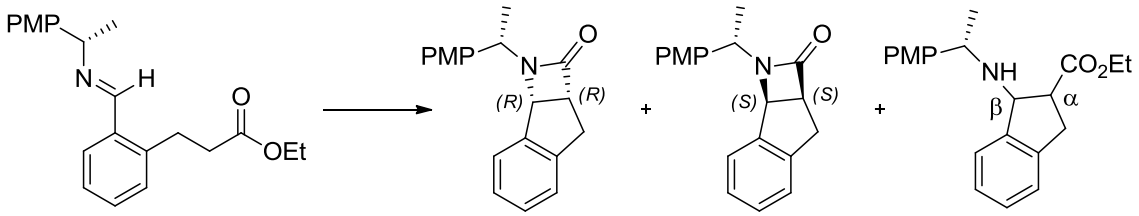


Figure 17- β-amino ester isolated from the enolate-imine cyclisation reaction

Analysis of the ^{1}H NMR spectra of the crude products revealed that using LiHMDS and KHMDS in THF at room temperature afforded the minor β-amino ester in the best yield. In comparison, using NaHMDS as a base does not generate the β-amino ester, with no β-amino ester being present in the ^{1}H NMR spectra for any of the optimization reactions carried out in Table 9.

The appearance of a minor β-amino ester is not completely unexpected when the work by Andrews *et al.* is considered,[132] where their original conditions using LiHMDS resulted in β-amino ester **205** being formed as the major product.

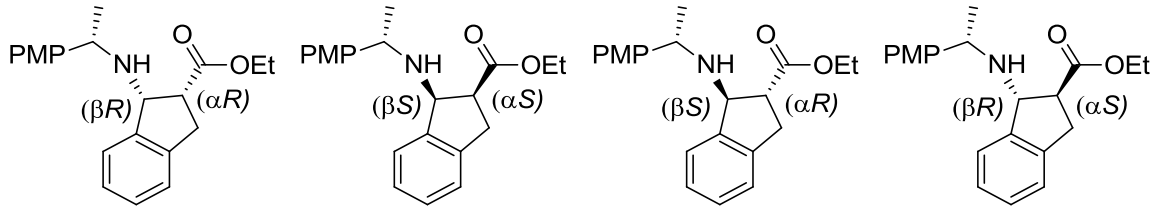
Table 9- Ratio of β-lactams and β-amino esters products in enolate-imine cyclisation reactions



221 **223a** **223b** **237**

Entry	Base (1.1 equiv.)	Temp (°C)	Solvent	Ratio of Products (223a:223b:237)
1	LiHMDS	rt	THF	49:18:33
2	KHMDS	rt	THF	30:31:39
3	KO^{t}Bu	rt	THF	65:35:0
4	NaHMDS	rt	THF	77:23:0

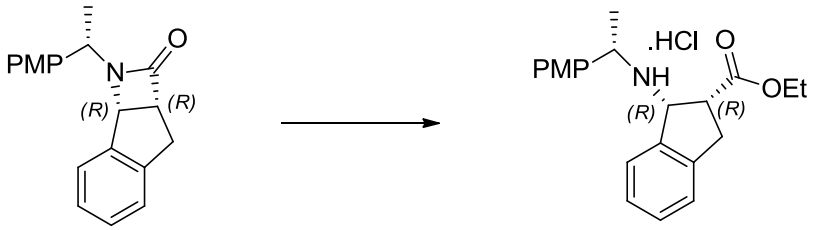
With the identification of a minor β-amino ester side product established, the next step was to establish its stereochemistry. There are four possible diastereomers which could potentially be assigned to β-amino ester **237** (Figure 18), so therefore the next step was to prepare authentic samples of all of these isomers for comparative purposes.



238 *Cis* 1 | **239** *Cis* 2 | **240** *Trans* 1 | **241** *Trans* 2

Figure 18- Possible diastereomers of unknown β-amino ester 237

At the outset, the major diastereomer of (*S*,α*R*,β*R*)-β-lactam **223a** was subjected to acidic conditions in ethanol, which resulted in a ring opening reaction to form the HCl salt of (*S*,α*R*,β*R*) β-amino ester **242** shown in Scheme 97.

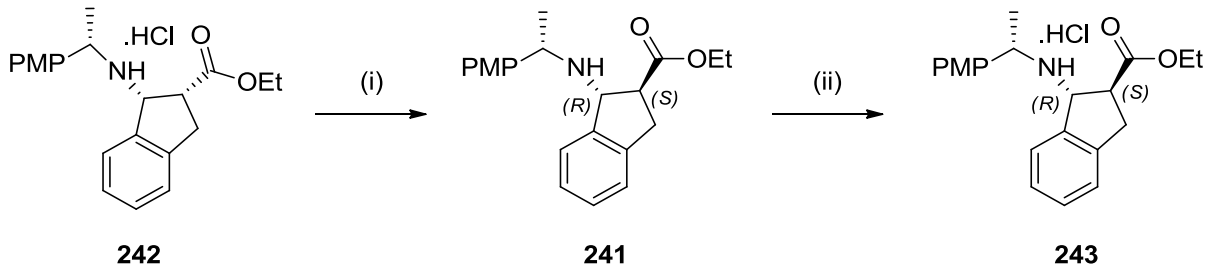


223a → **242** 93% Yield

Reagents & Conditions: HCl (1M in Et_2O), EtOH, reflux, 3 hrs

Scheme 97- Ring opening of (*S*,α*R*,β*R*)-β-lactam 223a

In order to obtain the *trans* isomer (*S*,α*S*,β*R*) **241** an epimerization reaction was performed on the *cis*-β-amino ester **242** using the methodology reported by Fulop *et al.* that had been used previously to epimerise a similar benzocispentacin structure.[126] Therefore, the HCl salt of the *trans* diastereomer was synthesised by stirring with NaOEt in EtOH followed by acidification with 1M HCl for 30 minutes which gave the (*S*,α*S*,β*R*)-diastereomer **243** (Scheme 100).

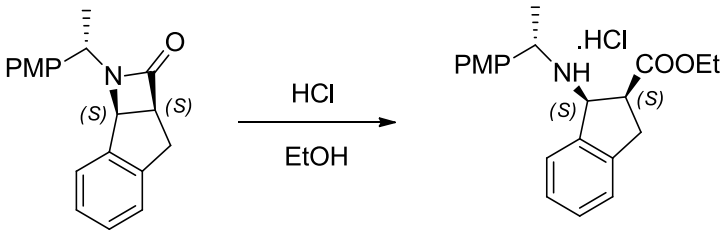


242 **241** **243**

Reagents & Conditions: (i) NaOEt, EtOH, reflux, 7 hrs; (ii) HCl (1M in Et_2O), rt, 0.5 hrs

Scheme 98- Synthesis of β-amino ester 243

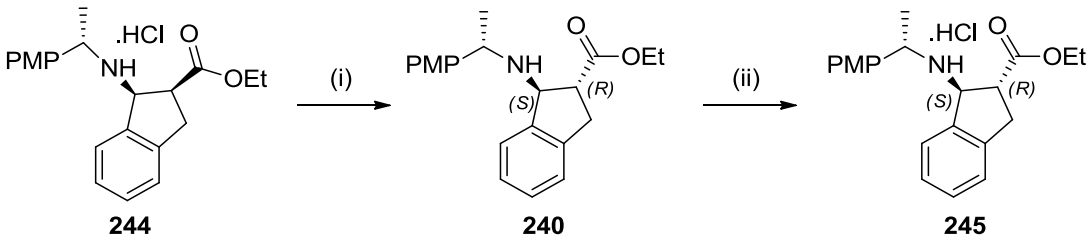
Next, the alternative β-amino ester *cis* diastereomer (*S*,α*S*,β*S*) **244** was synthesised from the (*S*,α*S*,β*S*) minor β-lactam diastereomer **223b**, that was isolated from an unselective cyclisation reaction. Previously established conditions using KHMDS as a base to carry out the enolate-imine cyclisation reaction on **221** had given an equal ratio of the two major and minor diastereomeric β-lactams **223a** and **223b** (Table 4). Therefore, the cyclisation reaction was repeated on a larger scale and the crude product purified by chromatography to afford an authentic sample of (*S*,α*S*,β*S*)-β-lactam **223b**. With the (*S*,α*S*,β*S*)-β-lactam in hand the subsequent acid catalysed ring opening reaction was carried out to afford the corresponding (*S*,α*S*,β*S*)-β-amino ester **244** (Scheme 99).[126]



223b **244**
96% Yield

Scheme 99- Ring opening of minor diastereomer of β-lactam 223b

Lastly, to obtain the fourth and final diastereomer of the β-amino ester, the *cis* (*S*,α*S*,β*S*)-β-lactam **244** was epimerized using NaOEt in EtOH, followed by stirring in 1M HCl for 30 minutes to afford the *trans*-(*S*,α*R*,β*S*)-β-amino ester **245** (Scheme 100).[126]



Reagents & Conditions: (i) NaOEt, EtOH, reflux, 48 hrs; (ii) HCl (1M in Et_2O), rt, 0.5 hrs

Scheme 100- Epimerisation of β-amino ester 244

With all four possible diastereomers in hand it was possible to compare their ^{1}H NMR spectra, focusing on the three diagnostic protons of their 5-membered rings (Figure 19).

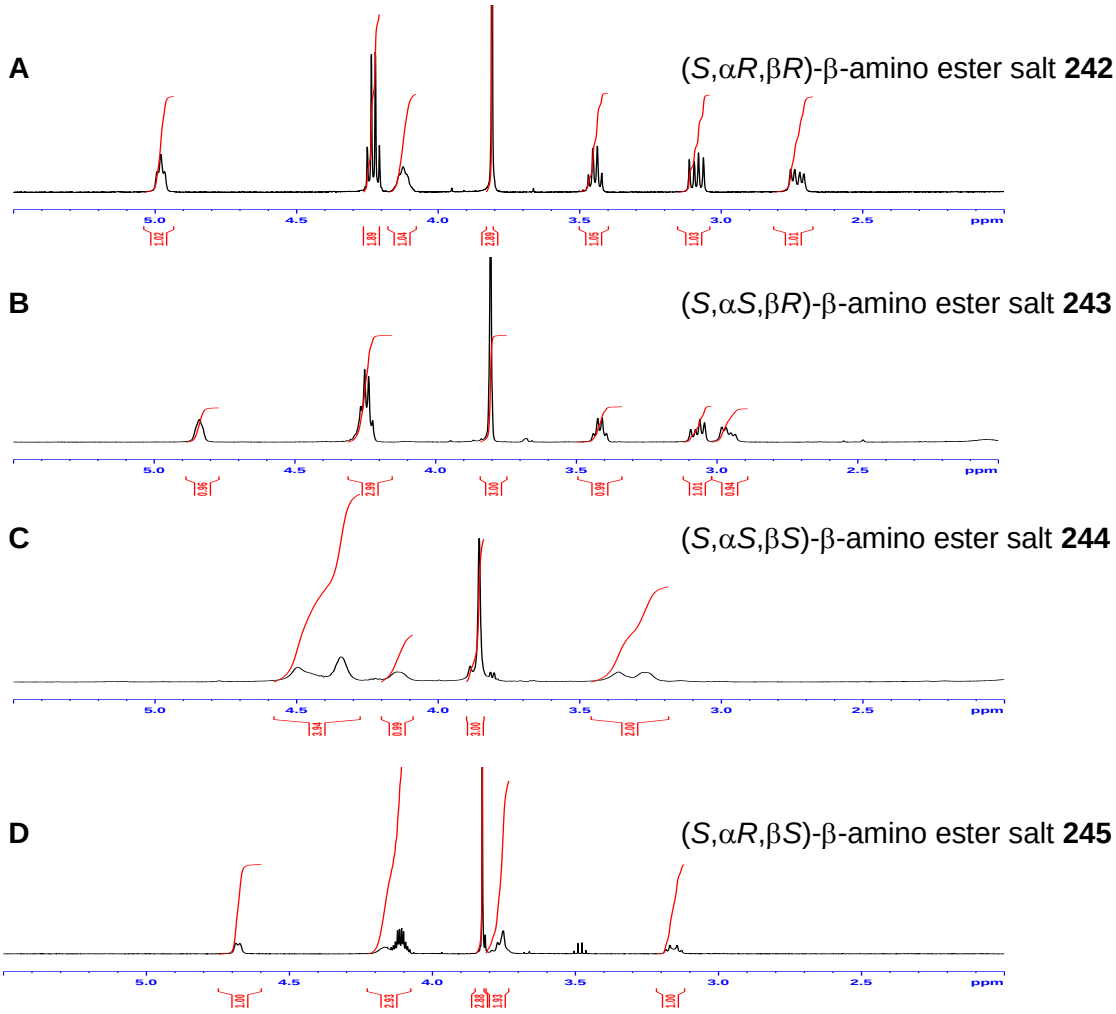
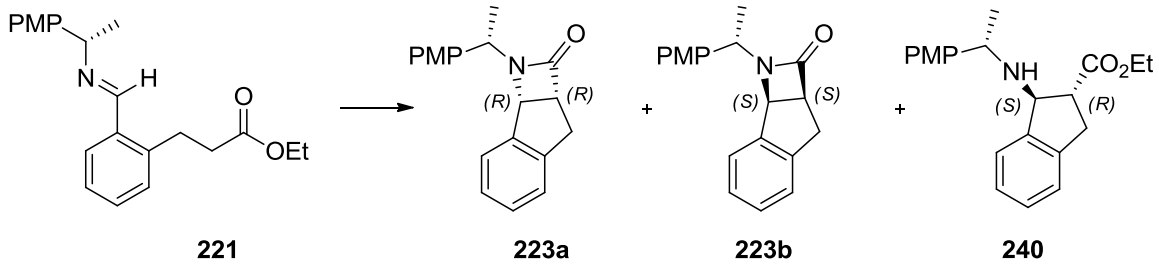


Figure 19- ^{1}H NMR spectrum of four β-amino ester diastereomers

Comparison of the four ^{1}H NMR spectra (Figure 19) showed that each diastereomer exhibited distinct resonances between 2.5 ppm and 5 ppm, with the ^{1}H NMR spectrum of (S,αS,βR)-β-amino ester **245** being identical to the ^{1}H NMR spectrum of the minor diastereomer isolated from the KHMDS enolate-imine cyclisation reaction. Therefore, based upon the ^{1}H NMR data we can revise the scheme shown in Table 9 to include the stereochemistry of the minor β-amino ester by-product (Scheme 101).



Scheme 101- All possible cyclisation products with relevant stereochemistry

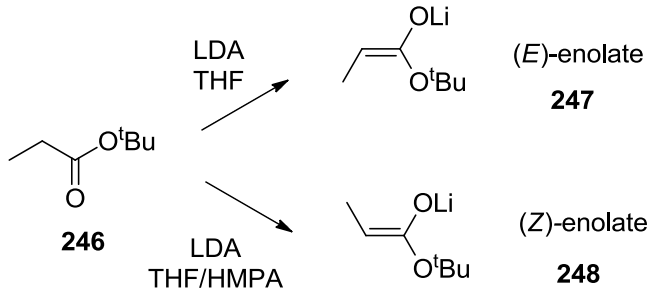
To conclude, the structure of the β-amino ester side product was determined as (1*S*,2*R*)-ethyl-1-(((*S*)-1-(4-methoxyphenyl)ethyl)amino)-2,3-dihydro-1H-indene-2-carboxylate, which enabled a complete picture of the stereochemical outcome of this cyclisation reaction to be obtained.

2.12 Rationale for the Stereochemistry of the Enolate-Imine Cyclisation Reaction

The formation and geometry of the enolate generated in these cyclisation reactions is a crucial factor in explaining the stereochemical outcome of β-lactam formation. There are two possible geometries when generating substituted enolates; either a (*Z*)-enolate or an (*E*)-enolate. Whereas the chiral auxiliary fragment determines the facial selectivity of the cyclisation reaction, the geometry of the enolate formed is highly significant since it determines the *cis*/*trans* diastereoselectivity of the initial stereodefining cyclisation reaction.

Literature precedent suggests that deprotonation of an ester with NaHMDS in THF (Scheme 96) should result in the formation of an (*E*)-enolate. In 1976, Ireland *et al.*[155]

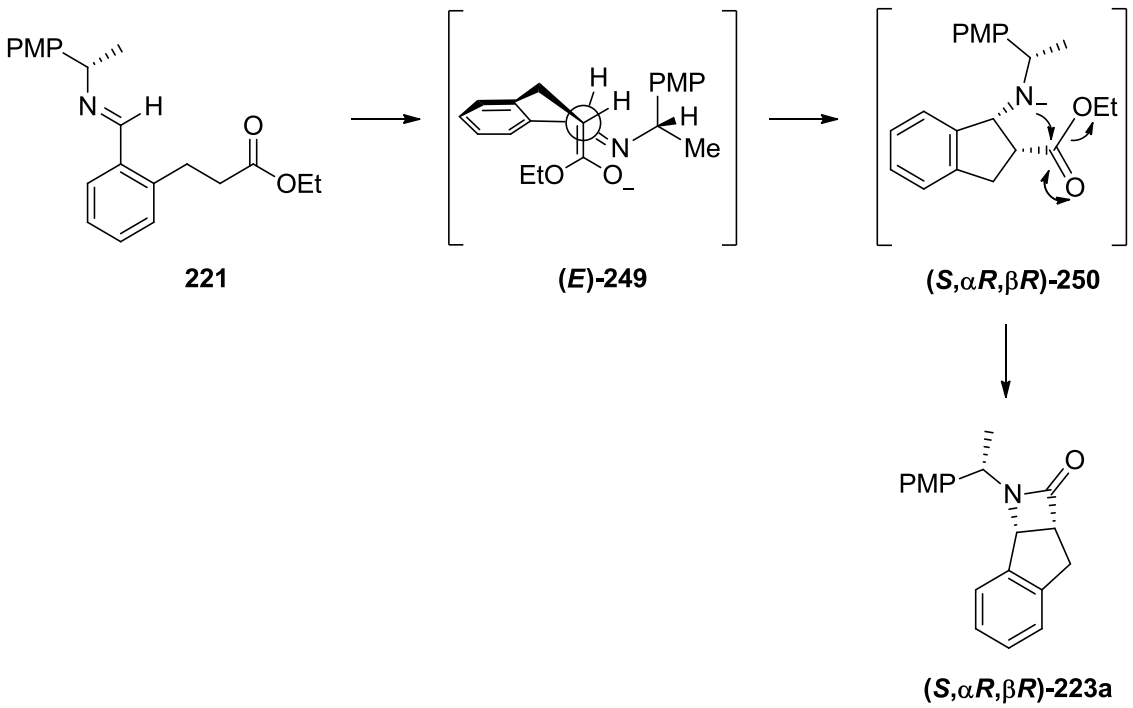
described how an appropriate base and solvent selection determines the geometry of the ester enolate formed, as part of their attempts to control the stereoselectivity of a subsequent [3,3] sigmatropic rearrangement. By trapping enolates of esters with *tert*-butyldimethylsilyl (TBDMS) groups it was shown that an (*E*)-isomer **247** was formed using LDA in THF (~ 95%).[156] However, when the solvent system was altered to include hexamethylphosphoramide (HMPA), the (*Z*)-enolate ester **248** was formed (~85%).[156] These findings were later confirmed by crystallographic data (Scheme 102).[157]



Scheme 102- Formation of (*Z*)/(*E*)-lithium ester enolates[155]

Further to this, research by Heathcock *et al*. showed that the percentage of (*Z*)-ester enolates generated by strong bulky bases like LDA is very low, with less than 5% of any (*Z*)-enolate being formed.[158] Therefore it can be concluded that an (*E*)-ester enolate should be generated during our intramolecular enolate-imine cyclisation reactions.

It has been demonstrated (Table 6) that the cyclisation of the sodium enolate onto the ω-imino ester produces the same β-lactam regardless of the presence of 15-crown-5. Therefore, this suggests that the initial 5-*exo*-trig reaction proceeds *via* a non-chelated open transition state (Scheme 103).



Scheme 103- Mechanism of enolate-imine cyclisation *via* an (*E*)-ester enolate

The next step was to consider the diastereomeric intermediates that could be formed in this cyclisation reaction and provide an explanation for the selective formation of the (*S*,α*R*,β*R*)-β-lactam **223a** as the major product. There are four possible diastereomeric *N*-anions that could potentially be formed in this 5-*exo*-trig cyclisation reaction (Figure 20).

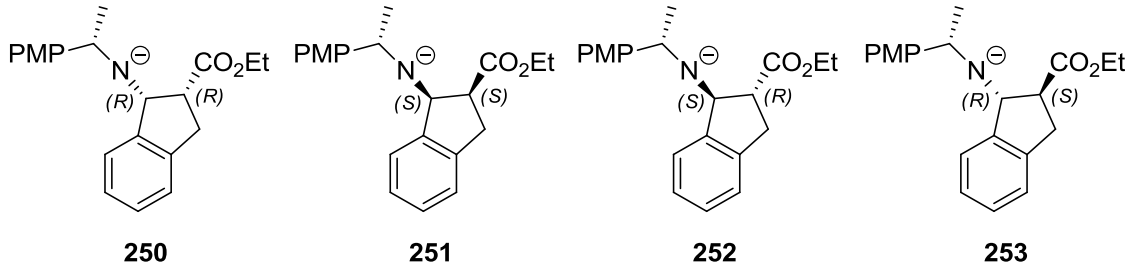


Figure 20- Possible *N*-anion intermediates after 5-*exo*-trig cyclisation

These diastereomeric intermediates will have different transition state energies of formation; with the epimerisation studies carried out in Scheme 98 clearly demonstrating that *trans* cyclic β-amino esters are more thermodynamically stable than their corresponding *cis* β-amino esters. In order to further understand the relative

energies some computational modeling was carried out on all four possible diastereomeric intermediates whose structures are presented in Figure 21-Figure 24, in an orientation viewed down the forming bond. The computational modeling and theoretical calculations were carried out by Dr. Andrew Leach at AstraZeneca with the programme “Gaussian09” being applied to the methyl ester diastereomers to minimize the number of calculations required.

In Figure 21, the lowest energy transition state conformation of the aza-anion **250** is shown which affords the observed (*S*,α*R*,β*R*) β-lactam **223a**. The key feature of this conformation is that the small benzylic hydrogen atom is presented towards the aza-anion fragment. This enables this conformation to minimise steric hindrance with the ester fragment, which results in an orientation whereby the methyl group of the chiral auxiliary fragment pointed downwards, with the more sterically demanding phenyl group pointing upwards. In comparison, Figure 22 illustrates the relatively disfavoured conformation of aza-anion **251** that leads to the formation of the minor (*S*,α*S*,β*S*) β-lactam **223b**. This intermediate **251** is largely disfavoured on steric grounds due to the chiral auxiliary phenyl group clashing with the ester fragment. Figure 23 shows the lower energy transition state leading to the *trans*-(*S*,α*R*,β*S*)-*N*-anion **252** where a staggered conformation is observed, in which the phenyl group of the auxiliary fragment has rotated so that it is staggered along the bond with the methyl substituent in the same plane as the methoxy group. In contrast, the disfavoured transition state in Figure 24 leading to *trans*-*N*-anion **253** results in its phenyl group being placed close to the methoxy group, and is therefore less likely to form.

Therefore based on computational calculations, the transition state energies leading to the *N*-anions of the diastereomeric β-amino esters **250**-**253** based upon their thermodynamic stability is as follows:

trans-(*S*,α*S*,β*R*) **253** < *trans*-(*S*,α*R*,β*S*) **252** < *cis*-(*S*,α*R*,β*R*) **250** < *cis*-(*S*,α*S*,β*S*) **251**

Pleasingly, this result is consistent with the fact that (*S*,α*R*,β*S*)-β-amino ester **240** was isolated as a minor component of the KHMDS and LiHMDS mediated cyclisation reactions. However, these relative energies lead to the question as to why we see formation of the (*S*-α*R*,β*R*) β-lactam **223a** as the major product of these cyclisation reactions?

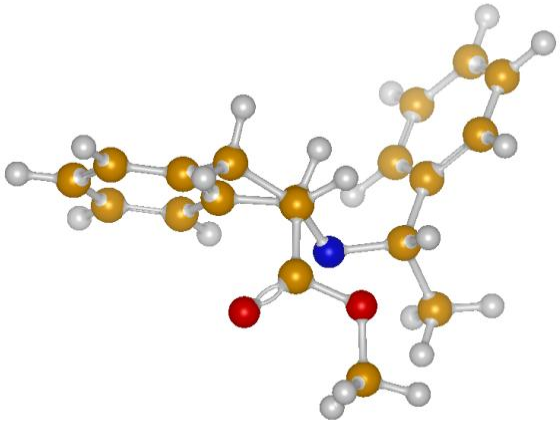


Figure 21- Favoured *cis*-*N*-anion structure enabling β-lactam formation 250

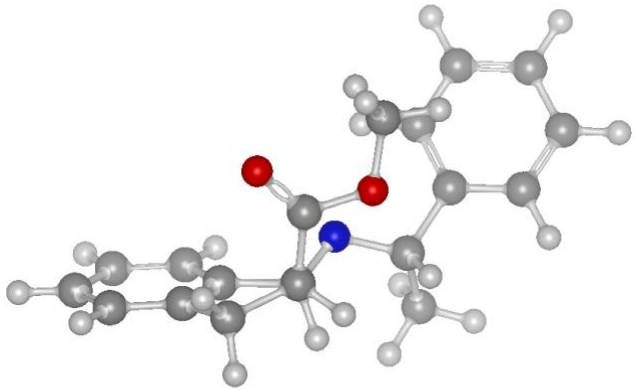


Figure 22- Disfavoured *cis*-*N*-anion structure enabling β-lactam formation 251

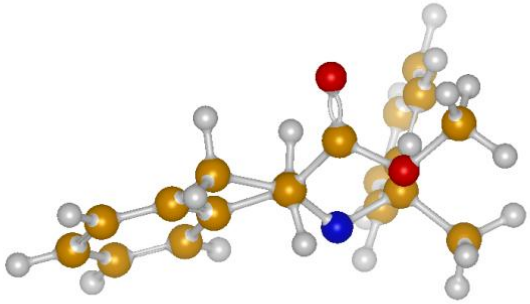


Figure 23-Favoured *trans*-*N*-anion structure 253

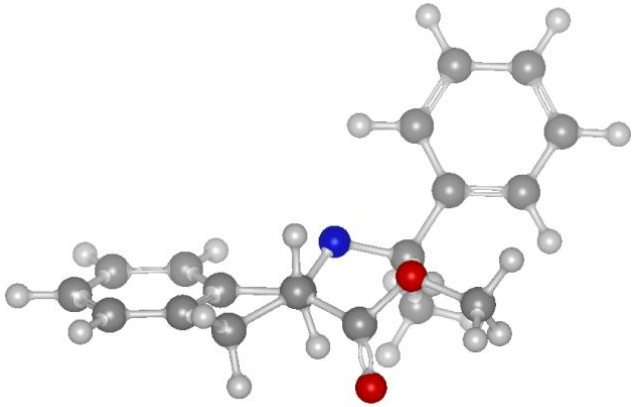
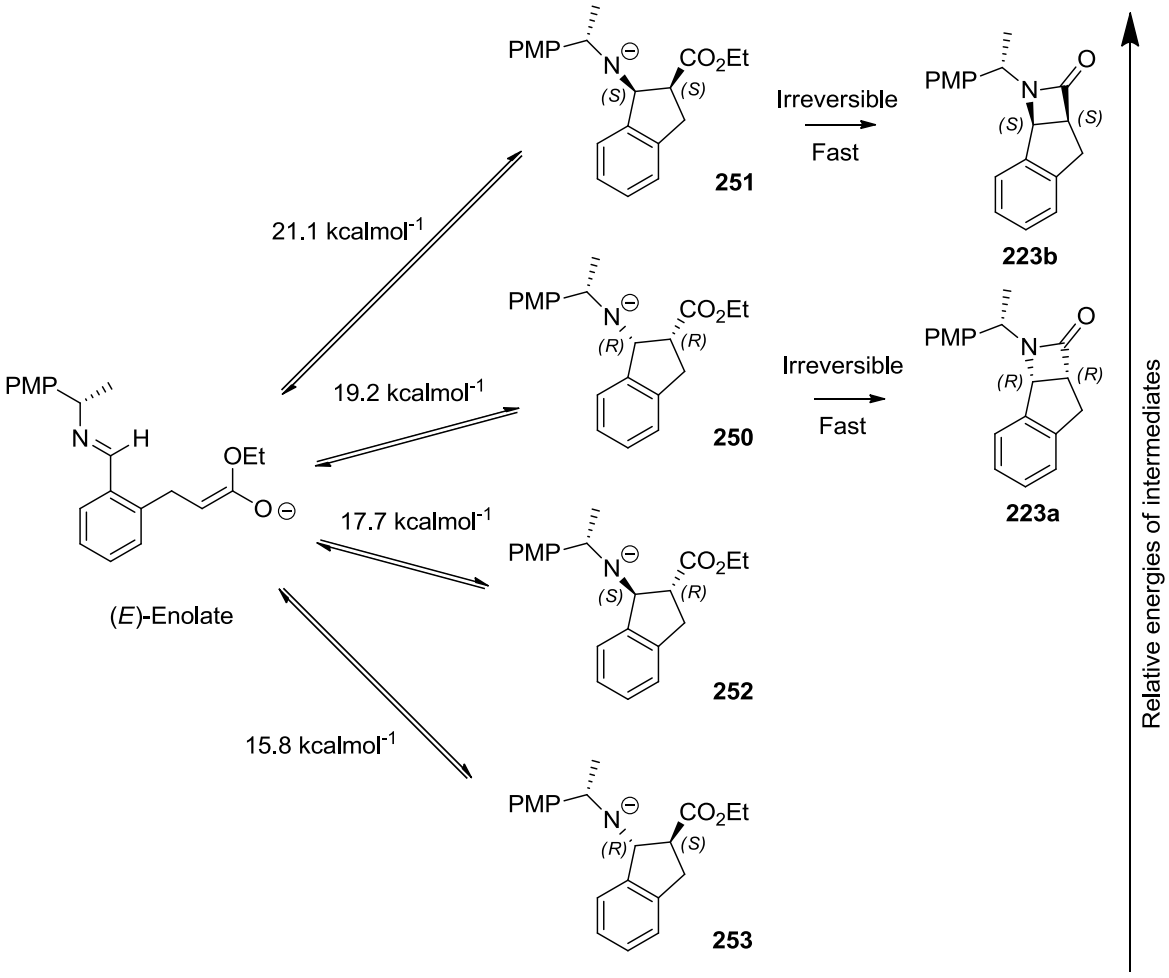


Figure 24-Disfavoured *trans*-*N*-anion structure 252

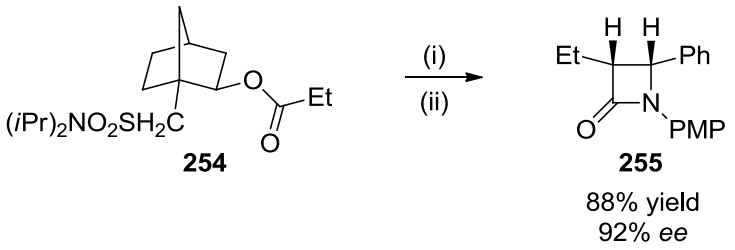
It is proposed that the answer to this question lies in the fact that the reaction must generate a dynamic equilibrium whereby a reversible enolate-imine cyclisation reaction occurs to afford a rapidly interconverting mixture of *trans/cis-N*-anions under thermodynamic control (Scheme 104).



Scheme 104- Molecular modelling of (*S*-α*R*,β*R*) β-lactam formation

Regardless of which of the thermodynamically stable *trans-N*-anions are formed there is no further ring closure pathway that the *trans-N*-anions (pK_a NH ~ 35) can undergo, therefore these intermediates can revert back to the enolate (pK_a enolate = 25) unless an adventitious proton source is present. Therefore, even though the cyclic *cis-N*-anions have a higher energy barrier of formation to overcome, the fact that they can undergo a subsequent rapid 4-*exo*-trig pathway, to irreversibly afford their corresponding β-lactams, leads to their selective formation. The formation of the

subsequent β-lactam, means that the equilibrium of the cyclisation reaction is then driven to produce more of the *cis*-*N*-anions until the reaction is complete. Therefore, (*S*-α*R*,β*R*) β-lactam **223a** is formed preferentially over the (*S*-α*S*,β*S*)-β-lactam **223b**, as formation of the *cis*-*N*-anion **251** is calculated to be several kcals higher, therefore less than 1% of this diastereomer would be expected to be observed. All computational calculations are based upon the assumption that the rate determining step is the enolate formation/cyclisation and not the rapid 4-*exo*-trig cyclisation affording the β-lactam. This assumption agrees with previously reported modeling studies on related intermolecular ester enolate-imine cyclisation reactions to afford β-lactams.[13] There are also several examples in the literature where lithium ester enolates have been reported to undergo intermolecular cyclisation reactions on to imines resulting in the selective formation of *cis*-β-lactams as seen in Scheme 105.[30,49-50,52]



Reagents & Conditions: (i) LDA, THF, -70°C to rt; (ii) N-benzylidene-4-methoxyaniline

Scheme 105- Intermolecular lithium ester enolate reaction forming *cis*-β-lactams[49]

To summarise, the intramolecular 5-*exo*-trig cyclisation reaction of (*E*)-enolate occurs under kinetic control to afford four possible *N*-anion intermediates under thermodynamic control. Despite the higher relative energies required for the formation of *cis*-*N*-anions, they are the only diastereomers that can undergo a subsequent 4-exo-trig ring closure, which then drives the equilibria of the reaction to give β-lactam products.

2.13 Benzocispentacin Conclusion

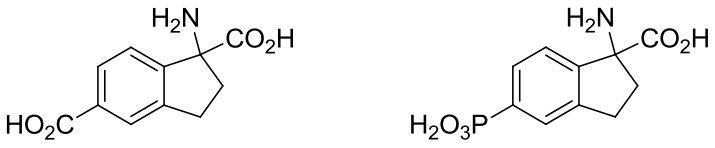
In conclusion, a chiral auxiliary strategy has been developed that enables an intramolecular ester enolate-imine cyclisation reaction to be used for the asymmetric synthesis of a tricyclic β-lactam **223a** with excellent levels of stereocontrol. The (*E*)-

enolate of an *N*-(α-methyl-*p*-methoxybenzyl)-ω-imino ester undergoes intramolecular 5-*exo*-trig cyclisation to afford a *cis*-*N*-anion, which subsequently undergoes a 4-*exo*-tet ring closure to furnish a tricyclic (*S*,α*R*,β*R*)-β-lactam **223a** in good yield and excellent *de*. An optimized protocol has been established using NaHMDS and a crown ether in THF, with potential side products in this reaction having been identified and their stereochemistry assigned. In the following section, application of this methodology for the asymmetric synthesis of a range of structurally related cyclic β-lactams will be described.

2.14 Development of Benzocispentacin Analogues

2.14.1 Previous Synthesis of Indane Derived Amino Acids

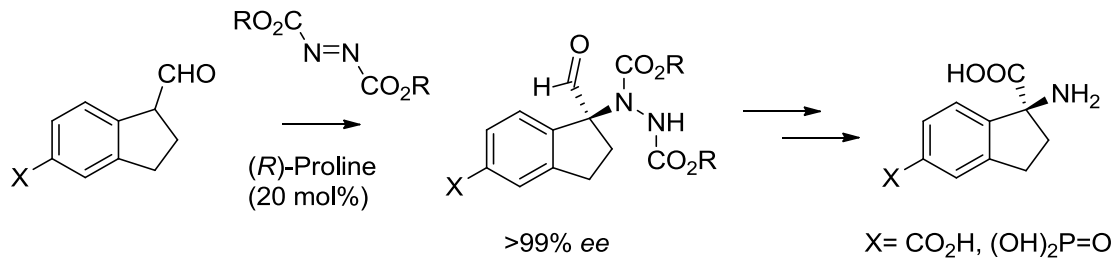
The availability of a versatile methodology to synthesise a range of highly functionalized cyclic β-amino acids is highly desirable. In particular, there is a large amount of interest in the synthesis of indane amino acid derivatives due to their potential biological properties. For example, certain substituted indanes have been shown to be mechanism-based inhibitors of dopamine β-hydroxylase.[159] In addition α-amino acids of substituted indanes, AIDA and APICA, have been shown to be antagonists of metabotropic glutamate receptors which are associated with neurological diseases (Figure 25).[160]



256 **257**

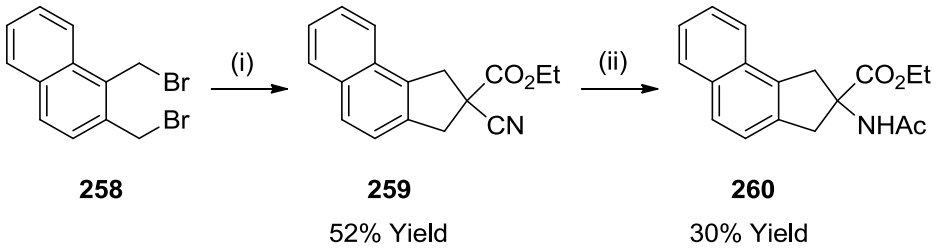
Figure 25- Structures of AIDA 256 and APICA 257

Due to their important biological activities there have been several attempts at preparing substituted indane amino acids, including an organocatalytic enantioselective synthesis using (*R*)-proline for the synthesis of both (*S*)-AIDA and (*S*)-APICA in 2005 (Scheme 106) .[161]



Scheme 106- Synthesis of (*S*)-AIDA and (*S*)-APICA

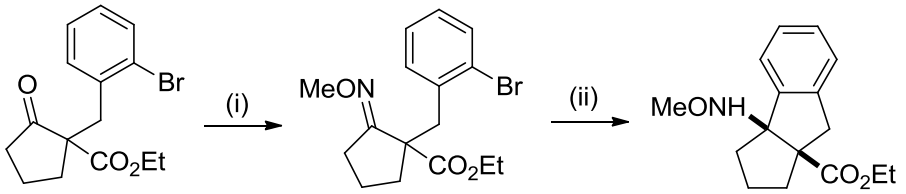
More recently in 2011, methodology for the synthesis of angularly fused indane amino acids was established,[162] with addition of ethyl isocyanoacetate to dibromoarene **258** resulting in construction of the new ring system of the tricyclic indane amino acid structure (Scheme 109).[162] These types of α-amino acids scaffolds have been widely used in recent years and the ability to access similar highly functionalized enantiopure analogues for benzocispentacin would be a welcome development.



Reagents & Conditions: i) Ethyl isocyanoacetate, K_2CO_3, MeCN; (ii) a) EtOH, dil. HCl; b) Ac_2O, DMAP, DCM

Scheme 107- Synthesis of fused indane α-amino acid derivatives[162]

Previously, it had been reported that the addition of enolates onto chiral imines does not provide good methodology for accessing highly substituted β-amino acids.[163] Despite this, there have been several other reported methods to generate substituted indane β-amino acids (benzocispentacin). This includes the cyclisation of radical species onto oxime ethers with tributyltin hydride being used as a radical initiator to afford the *cis*-alkoxyamine **263** in 68% yield (Scheme 108).[164]

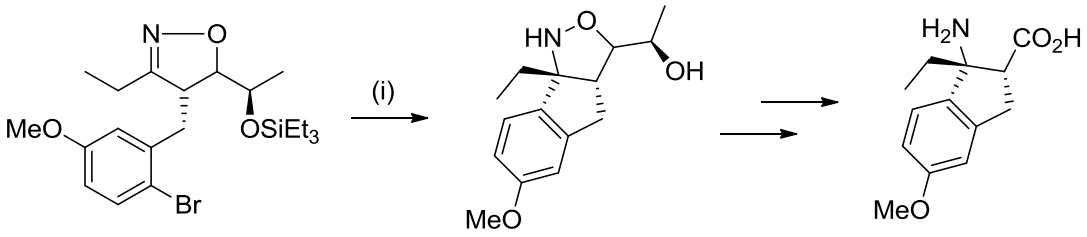


261 **262** 84% Yield **263** 68% Yield

Reagents & Conditions: (i) $MeONH_2$.HCl, pyridine, rt; (ii) Bu_3SnH, AIBN, benzene, reflux

Scheme 108- Synthesis of alkoxyamino-3-methylidene-chromanes[164]

Furthermore in 2005, diastereoselective addition of an aryl anion to a chiral isoxazoline fragment generated benzocispentacin structures containing four contiguous stereocentres was reported.[163] In particular, the generation of a quaternary centre in **266** is highly valuable and therefore these types of highly functionalized structures have great potential as peptidomimetic scaffolds (Scheme 109).

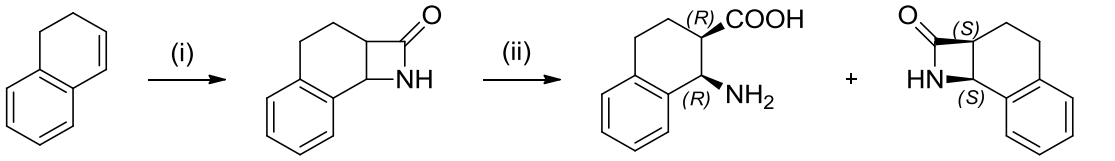


264 **265** 93% Yield **266**

Reagents & Conditions: (i) a) ^tBuLi, THF, -78°C; b) HCl/H_2O, 0°C to rt

Scheme 109- Synthesis of disubstituted β-amino acids from chiral isoxazolines[163]

As discussed earlier, one of the most useful methodologies for the synthesis of polycyclic β-amino acids has been developed by Fulop *et al.*, who have successfully managed to use the enzyme Lipolase to catalyse the kinetic resolution of racemic β-lactam **268** as shown in Scheme 110.[126] Such work has provided a range of cyclic structures, but this methodology could not be used to prepare chiral β-lactams containing aryl substituents due to the substrate specific nature of the enzymes active site.

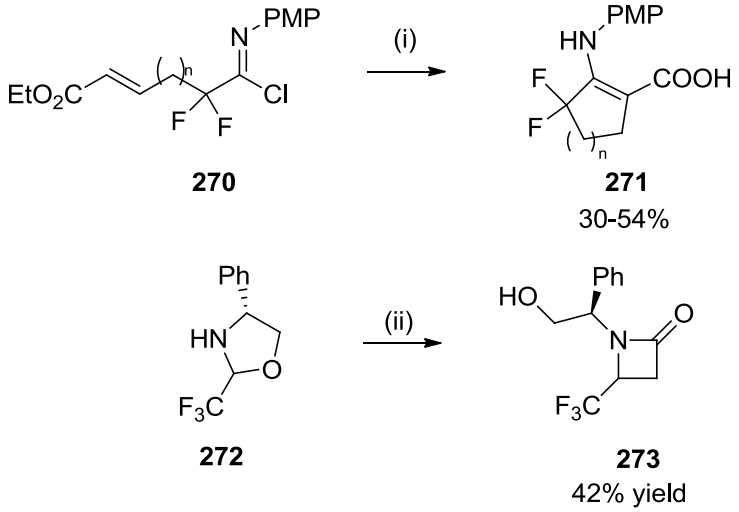


267 **268** 78% Yield **269** 45% Yield **268b** 45% Yield

Reagents & Conditions: (i) CSI, Na_2SO_3; (ii) H_2O, Lipolase, 60°C

Scheme 110- Synthesis of benzocishexacin using enzymatic resolution[126]

Another highly researched area is the synthesis of fluorinated β-amino acids that are important medicinal chemistry targets.[165] There are many examples of the incorporation of fluorine into cyclic β-amino acids which has recently been the subject of a large review.[165] For example, the synthesis of a difluorinated analogue of cispentacin **271**[166] and substituted β-lactam **273**[167] has generated a large amount of research interest (Scheme 111).



270 **271** 30-54%

272 **273** 42% yield

Reagents & Conditions: (i) a) H_2, Pd/C; b) LDA, THF, -78 °C; (ii) $BrCH_2COEt$, Zn, THF, reflux

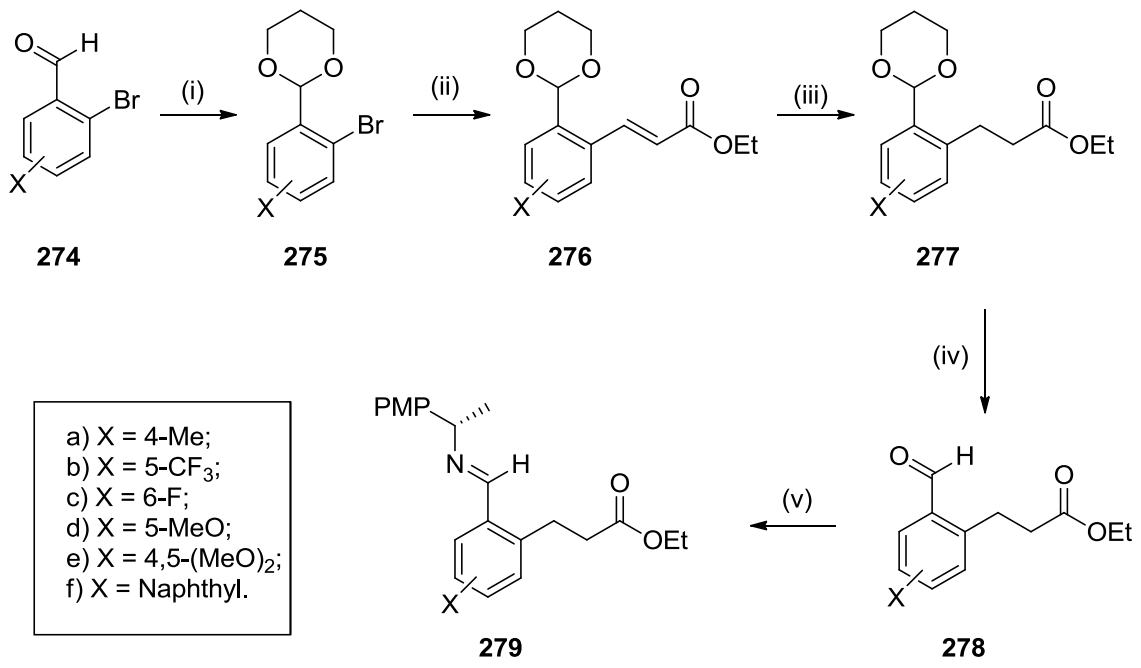
Scheme 111- Examples of fluorinated β-amino acids/β-lactams[166-167]

Therefore, it was the aim of this work to develop our enolate-imine cyclisation reaction to prepare highly functionalized benzocispentacin analogues that incorporated methyl, methoxy and fluoro substituents as well as an angularly fused naphthyl indane β-

lactams which could mirror products previously shown to be valuable for α-amino acid research.

2.14.2 Synthesis of Benzocispentacin Analogues

Six commercially available substituted 2-bromobenzaldehydes were subjected to the previously developed 5-step methodology to furnish their corresponding chiral ω-imino-esters in moderate to good yields. These cyclisation substrates were derived from 2-bromo-4-methylbenzaldehyde **274a**, 2-bromo-5-(trifluoromethyl)benzaldehyde **274b**, 2-bromo-6-fluorobenzaldehyde **274c**, 2-bromo-5-methoxybenzaldehyde **274d**, 2-bromo-4,5-dimethoxybenzaldehyde **274e** and 1-bromo-2-naphthaldehyde **274f**. The most significant alteration to the synthetic protocol was the conjugate reduction of the double bond of the naphthyl derivative **277f** that required 72 hours instead of the 48 hours employed for the other analogues. Apart from this exception, all of the other reactions proceeded effectively to afford the desired cyclisation substrates (Scheme 112).

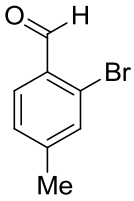
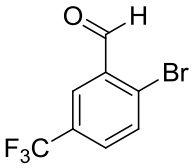
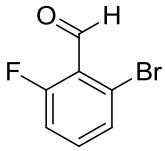
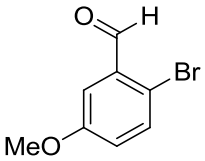
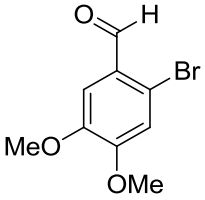
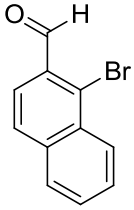


Reagents & Conditions: (i) Propan-1,3-diol, pTSA, Toluene, (ii) Ethyl Acrylate, $Pd(OAc)_2$, $(o\text{-}Tol)_3P$, DIPEA, MeCN (iii) $NaBH_4$, $CoCl_2 \cdot 6H_2O$, Ethanol (iv) Acetic acid and water (v) (S)-(-)-4-methoxy-α-methylbenzylamine, $MgSO_4$, DCM

Scheme 112- Synthesis of ω-imino esters (*S*)-279a-f

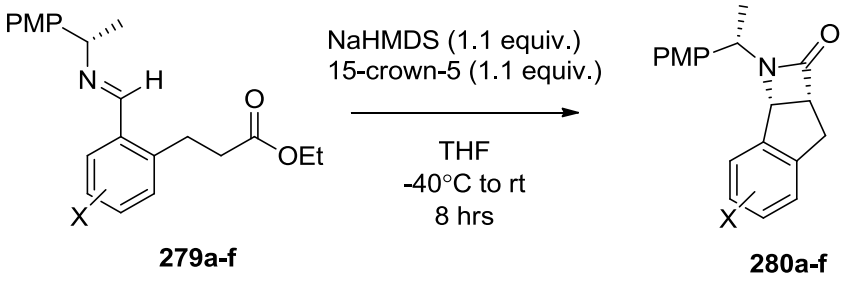
The yields obtained for each step of the synthetic protocol used to prepare six ω-imino esters **279a**-**f** can be seen in Table 10, which ranged from good to excellent.

Table 10- Yields obtained for the synthesis of chiral imino esters 279a-f

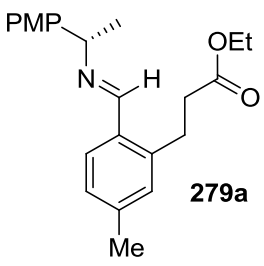
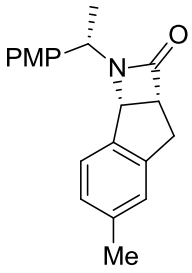
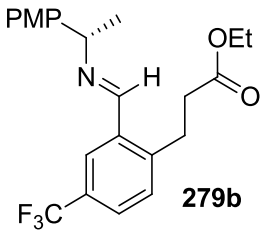
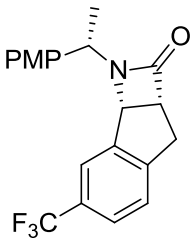
	Acetal 275 (%)	α,β-unsaturated ester 276 (%)	Saturated Ester 277 (%)	Aldehyde 278 (%)	Imine 279 (%)
	85	71	70	73	82
	79	68	54	69	85
	50	81	49	79	82
	96	58	71	86	85
	84	76	87	77	93
	84	84	75	71	92

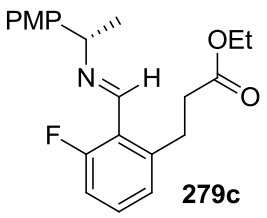
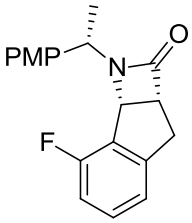
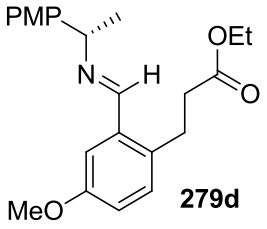
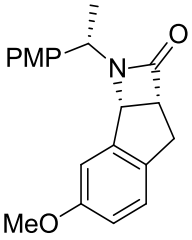
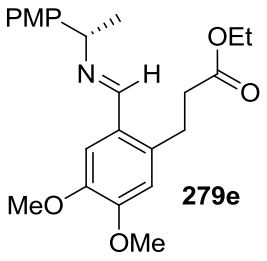
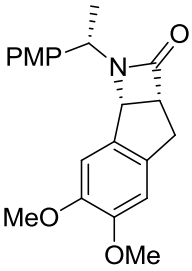
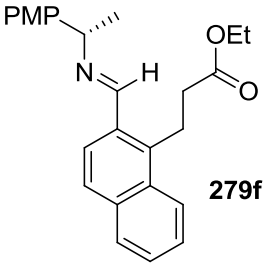
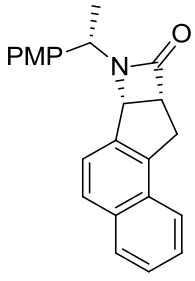
The intramolecular enolate-imine cyclisation conditions were then applied to the range of chiral ω-imino esters (**279a-f**) with the resulting *de*'s and yields obtained shown in Table 18. The *de*'s were determined from the integration of the diagnostic resonances for the major and minor β-lactam diastereomers (**280a-f**) in the ^{1}H NMR spectra of the crude reaction products. Cyclisation substrates containing a range of electron donating (Table 10, Entries 1, 4 and 6) and electron withdrawing (Table 10, Entries 2, 3 and 6) substituents in various ring positions, afforded a range of β-lactams using this methodology. As can be seen from Table 11, the majority of the substrates gave cyclised β-lactams with excellent *de*'s (>95%) and moderate to good yields. One exception is Entry 3 which had a notably lower *de* of 90% when the fluorine is *ortho* to the imine substituent, although this reaction does benefit from a much higher yield.

Table 11- Asymmetric synthesis of (*R,R*)-β-lactams 280a-f



279a-f **280a-f**

Entry	Substrate	Product	Yield (%)	*de* (%)
1	 **279a**	 **280a**	59	99
2	 **279b**	 **280b**	69	99

Entry	Substrate	Product	Yield (%)	*de* (%)
3	 **279c**	 **280c**	79	90
4	 **279d**	 **280d**	62	96
5	 **279e**	 **280e**	60	98
6	 **279f**	 **280f**	41	95

The X-ray crystallographic structure of one of the analogues, trifluoro-aryl-β-lactam **280b**, was obtained after successful recrystallisation from a mixed solvent of

dichloromethane and hexane. As shown in Figure 26, the X-ray crystal structure of the protected β-lactam **280b** shows that the major diastereomer of the enolate-imine cyclisation reaction is the (*S*,α*R*,β*R*)-β-lactam, where the methyl group on the auxiliary (C13) lies in the same plane as the β-lactam ring (C3-N1 and C2-C1) with the three hydrogen atoms on C2, C3 and C12 all pointing out of the plane of the paper in the same direction (as drawn, Figure 26).

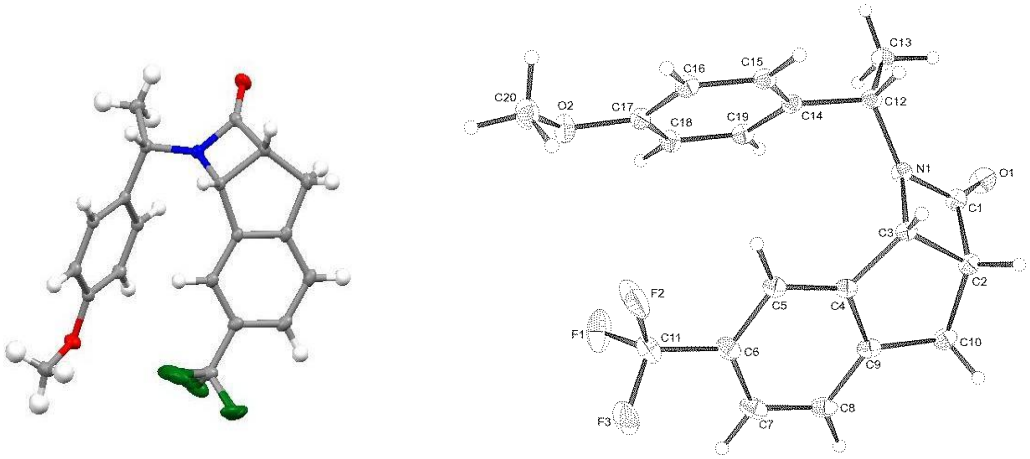


Figure 26- X-ray crystal structure of (*S*,α*R*,β*R*)-trifluoro-aryl-β-lactam 280b with ellipsoids drawn at the 50% probability level

Oxidative cleavage of the chiral auxiliary fragment of *N*-aryl-β-lactams **280a-f** was then carried out using CAN in MeCN/H_2O to afford the deprotected β-lactams **281a-c** in good yields under mild conditions (Figure 27).

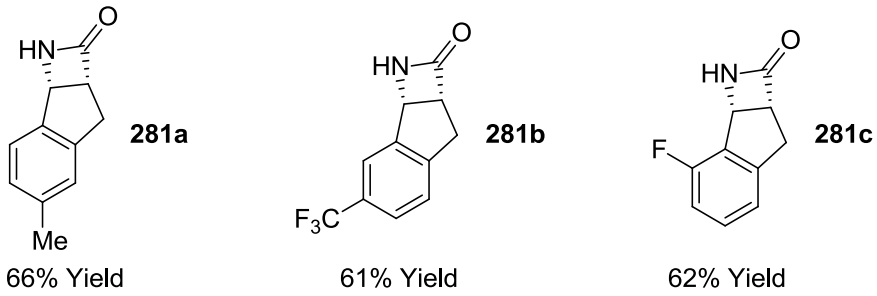
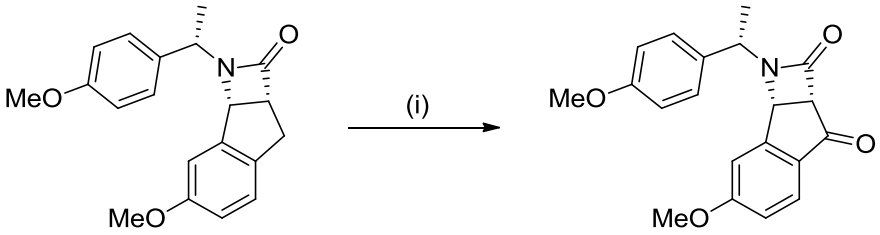


Figure 27- Synthesis of tricyclic β-lactam analogues

Attempts to remove the chiral auxiliary of the remaining three protected β-lactams **280d-f** proved unsuccessful. Firstly, treatment of the protected β-lactam **280d** with CAN gave a ^{1}H NMR spectrum that showed a number of products with the main component

from the deprotection reaction being identified as a keto-β-lactam. This product is formed from benzylic oxidation, instead of cleavage of the chiral auxiliary from the β-lactam ring. A similar benzylic oxidation was also observed for the structurally related *N*-aryl-β-lactam **280e** (Scheme 113).

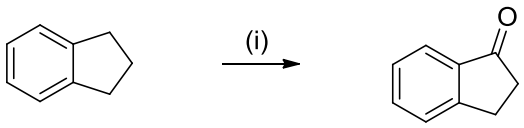


280d **282**

Reagents & Conditions: (i) CAN (3.0 equiv.), MeCN-H_2O (5:1), rt, 16 hrs.

Scheme 113- Formation of keto-β-lactam 282

A review of the literature revealed that the formation of such keto-β-lactams was not entirely unexpected, since CAN mediated benzylic oxidations of indane systems have been reported previously (Scheme 114).[168]



283 **284**
78% Yield

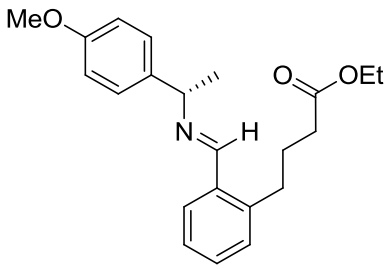
Reagents & Conditions: (i) CAN, HNO_3, 30°C, 1.5hrs

Scheme 114- Partial oxidation with CAN[168]

The naphthyl analogue **280f** was also not deprotected successfully, yielding only small amounts of starting material and a range of other unidentifiable products. Therefore, the current methodology for the removal of the chiral auxiliary is not suitable for *N*-aryl protected β-lactams **280d-f** and further work will be required to investigate alternative deprotection conditions for these analogues. Alternatively, a different auxiliary might be used to control the stereoselectivity of the cyclisation reaction.

2.14.3 Synthesis and Optimization of the Asymmetric Synthesis of Benzocishexacin

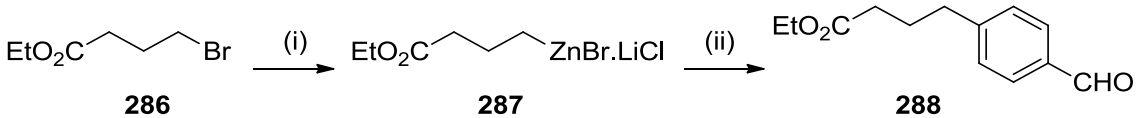
With a range of benzocispentacin derived analogues having been prepared the next step was to attempt to increase the acyclic ring size of the ω-imino ester that would cyclise to afford a six membered β-lactam. In order to prepare the desired ω-imino ester the design of an alternative synthetic protocol was required, such as an extra methylene group which would need to be included in the ester side chain (Figure 28).



285

Figure 28- Target starting material for benzocishexacin synthesis

Whereas previously a Heck cross coupling reaction of 2-bromobenzaldehyde had been used to install the ester C_3 side-chain, an alternative cross coupling methodology was required for addition of a longer C_4 side-chain. To address this problem a review of the literature revealed there was precedent for such a transformation, whereby Sase *et al.* had reported a one pot Negishi cross coupling reaction of aryl halides with alkyl zinc reagents.[169] In a two step reaction that involved the use of a PEPPSI ligand, a high yielding cross coupling procedure was used to furnish ethyl 4-(4-formylphenyl)butanoate **288** in an 87% yield (Scheme 115).[169]



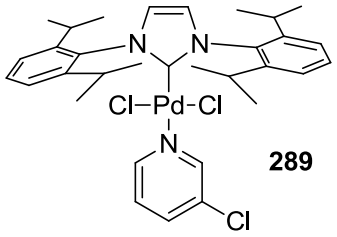
286 **287** **288**

87% Yield

Reagents & Conditions: (i) LiCl, Zn, dibromoethane, trimethylsilylchloride, iodine, THF, 50 °C, 12hrs; (ii) 4-bromobenzaldehyde, PEPPSI, DMI, rt, 1 hr

Scheme 115- One pot Negishi reaction using alkyl zinc intermediates[169]

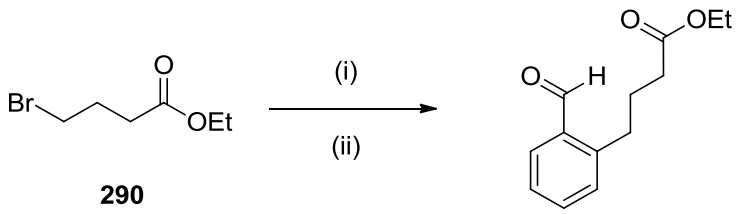
PEPPSI **289** (Pyridine-Enhanced Precatalyst Preparation, Stabilisation and Initiation), is a particularly useful ligand for these types of cross-coupling reactions, as it is easily synthesized, air stable and highly active, and has shown an increase in the scope and reliability of the Negishi reaction (Figure 29).[170]



289

Figure 29- Structure of PEPPSI ligand[170]

It was proposed that this methodology could be utilized to obtain the desired *ortho*-substituted ester. If possible, this technique would reduce the number of steps required for its synthesis when compared with benzocispentacin, since there would be no need to reduce a double bond or to protect the aldehyde functionality. As such, the one pot Negishi cross coupling was attempted using 2-bromobenzaldehyde **209** (Scheme 116), successfully affording ethyl 4-(2-formylphenyl)butanoate **291** in 51% yield. The only alteration to the original methodology was to extend the reaction time of the cross coupling reaction to 12 hours.



290

291

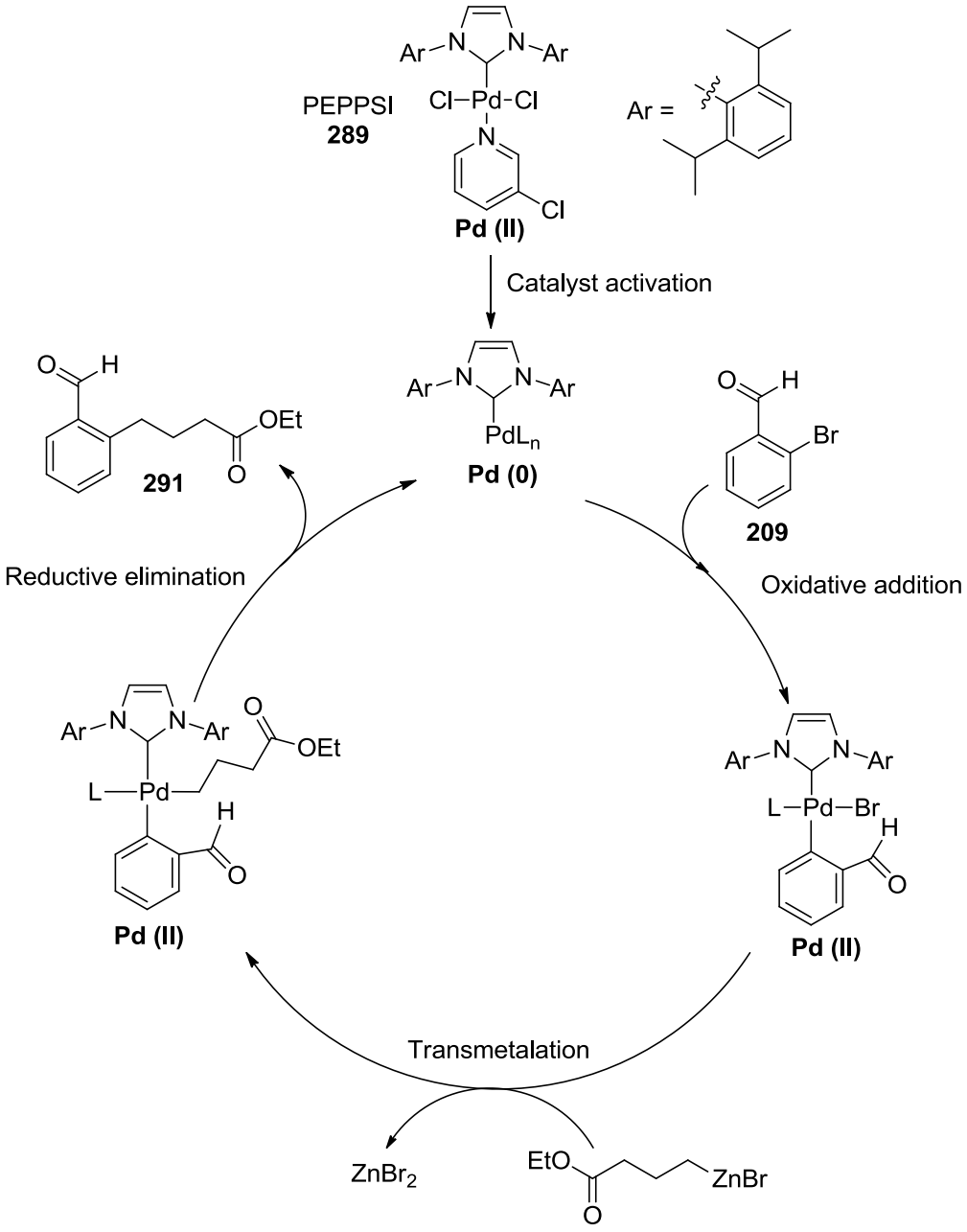
51% Yield

*Reagents & Conditions: (i) Lithium chloride, zinc, dibromoethane, trimethylsilylchloride, iodine, THF, 50 °C, 12hrs; (ii) 2-bromobenzaldehyde **209**, PEPPSI **289**, DMI, rt, 12 hrs*

Scheme 116- Synthesis of ethyl 4-(2-formylphenyl)butanoate from Negishi cross coupling

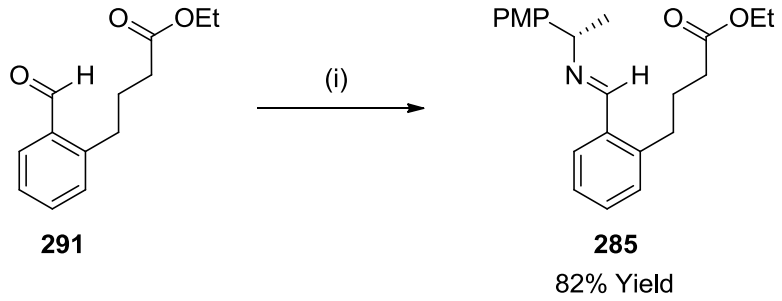
This cross coupling reaction starts with the active Pd(0) complex which adds to the aryl halide **209** *via* an oxidative addition, with the resulting Pd(II) complex subsequently undergoing transmetalation with the zinc activated ethyl 4-bromobutanoate. This is then

followed by a reductive elimination reaction which gives the desired product **291**, while regenerating the Pd(0) complex, as shown in Scheme 117.



Scheme 117- Proposed Negishi cross coupling reaction[169]

The next step was the formation of the chiral imino-ω-ester *via* reaction of the aldehyde functionality **291** with (*S*)-(-)-4-methoxy-α-methylbenzylamine under our standard conditions (Scheme 118).

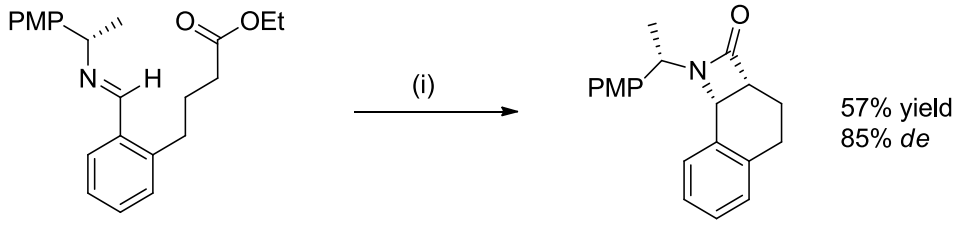


291 **285**
82% Yield

Reagents & Conditions: (i) (S)-(-)-4-methoxy-α-methylbenzylamine, $MgSO_4$, DCM, rt, 5hrs

Scheme 118- Synthesis of (*S,E*)-ethyl 4-(2-(((1-(4-methoxyphenyl)ethyl)imino)methyl)phenyl) butanoate

With the chiral imino-ω-ester in hand, it was decided that the optimized conditions previously established for the benzocispentacin derivatives (Scheme 96) would be applied to the first synthesis of the benzocishexacin β-lactam **292**. The cyclisation reaction of **285** proved successful, with the (*E*)-enolate undergoing a 6-*exo*-trig intramolecular cyclisation reaction by nucleophilic attack on to its chiral imine fragment. This gives a *cis*-aza-anion which subsequently performs a 4-*exo*-trig ring closing reaction resulting in the formation of β-lactam **292**. The β-lactam was generated in a moderate yield of 57% and a good *de* of 85%. In an attempt to improve the yield and *de* further a brief optimization screen was then carried out (Table 12).



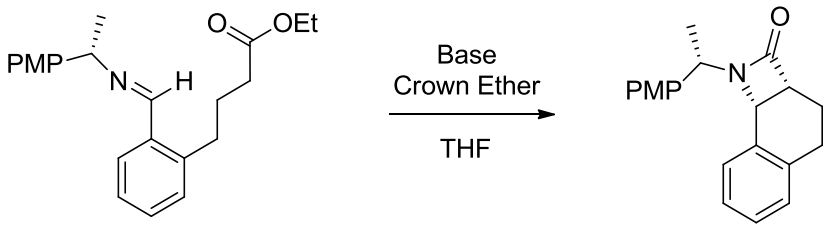
285 **292**

Reagents & Conditions: (i) NaHMDS (2.0 equiv.), 15-crown-5, THF, -45 °C to rt, 8 hrs

Scheme 119- Cyclisation reaction of chiral imino-ω-ester 292 to afford β-lactam 292

Initially, the cyclisation reaction was attempted with both LiHMDS and NaHMDS (Table 12, Entry 1 and 2) without the crown ether to see if this made any improvement. The results show that both the *de* and conversion were much lower than when compared with the previously optimized conditions (Table 12, Entry 7). When the crown ether was added at room temperature (Table 12, Entry 3) there was a clear increase in the conversion rate and *de*. Furthermore, when the temperature was decreased (Table 12, Entries 4 and 5) there was a decrease in the conversion rate, but a significant increase in the *de*, apart from when the reaction was carried out at -78 °C which gave only recovered starting material. The increase of base from 1.1 equivalents (Table 12, Entry 5) to 2.0 equivalents (Table 12, Entry 7) showed an impressive increase in the conversion, which may have been due to the presence of water in the reaction media which could have quenched the base when only 1.1 equivalents was used. Therefore, the best conditions established for this reaction are those of Entry 7, which were the initial conditions originally established in benzocispentacin synthesis.

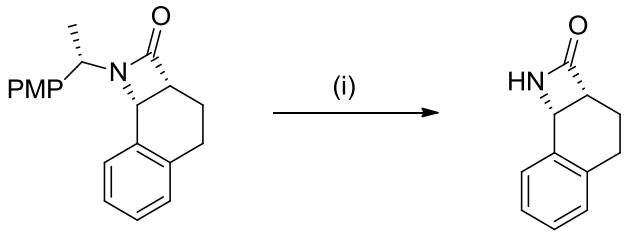
Table 12- Optimisation of a 6-*exo*-trig intramolecular enolate-imine cyclisation reaction



Entry	Base	Temp (°C)	Equiv.	Crown	Conversion (%)	*de* (%)
1	LiHMDS	rt	1.1	No	74	35
2	NaHMDS	rt	1.1	No	13	28
3	NaHMDS	rt	1.1	Yes	100	49
4	NaHMDS	0 to rt	1.1	Yes	62	58
5	NaHMDS	-40 to rt	1.1	Yes	44	84
6	NaHMDS	-78 to rt	1.1	Yes	0	-
7	NaHMDS	-40 to rt	2.0	Yes	73	85

The explanation for the decrease in the yield and *de* for the formation of β-lactam **292** must be due to the presence of the extra methylene unit. Once the (*E*)-enolate has been formed there must be more conformational mobility between the enolate fragment and the imine substituent, resulting in less stereocontrol of the initial 6-*exo*-trig cyclisation reaction, which results in a poorer facial selectivity and a lower *de*.

After purification by chromatography, the final step in the synthesis involved removal of the chiral auxiliary from *N*-aryl-β-lactam **292** by applying the CAN mediated oxidative deprotection shown in Scheme 92. The free β-lactam **293** was obtained in a 72% yield (Scheme 120), which may then undergo subsequent acidic hydrolysis to generate the corresponding β-amino acid as required.



292 **293**

72% Yield

Reagents & Conditions: (i) CAN (3.0 equiv.), MeCN-H_2O (5:1), rt, 16 hrs

Scheme 120- Oxidative cleavage of chiral auxiliary

To summarise, an alternative methodology has been devised for the synthesis of the 6-membered β-lactam **293**. The synthetic route to the cyclisation precursor is much shorter than the one used for the synthesis of its 5-membered analogues due to the use of a Negishi cross coupling reaction. This approach directly incorporates the ester side chain onto the aryl ring without the need for any protecting groups and the removal of a double bond. Although the 6-*exo*-trig enolate-imine cyclisation reaction occurs in acceptable yield and a good *de*, it does not proceed with the same level of diastereocontrol previously demonstrated for the 5-membered benzocispentacin analogues.

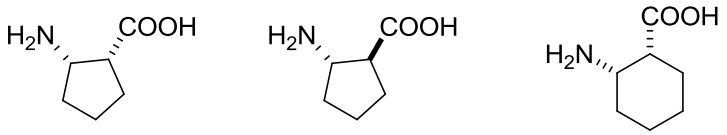
2.14.4 Conclusion

The application of the newly developed intramolecular enolate-imine cyclisation reaction for the synthesis of tricyclic β-lactams has been achieved to furnish seven novel polycyclic β-lactam analogues. The yields obtained range from moderate to high and the *de*'s range from good to excellent. There is a problem with the oxidative removal of the chiral auxiliary fragment for a few *N*-aryl-β-lactams but ultimately this novel enolate-imine cyclisation methodology was shown to be successful for the asymmetric synthesis of polycyclic β-lactam ring systems.

3 Results & Discussion- Acyclic Substrates

3.1 Introduction

The original aim of developing stereoselective methodology for carrying out an intramolecular enolate-imine cyclisation reaction had been achieved for a series of benzocispentacin substrates. An exciting application of this research would be to apply this methodology for the asymmetric synthesis for a range of chiral monocyclic β-amino acids. The most commonly reported monocyclic β-amino acids used for foldamer synthesis are cispentacin **294** and transpentacin **295**, which are also known as 2-aminocyclopentanecarboxylic acids (ACPCs) (Figure 30).



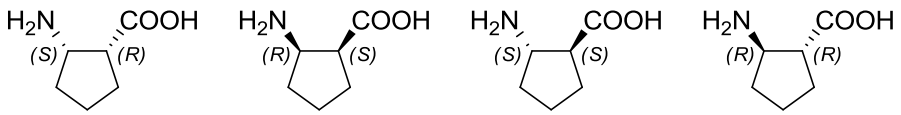
294 **295** **296**

Figure 30- Examples of cispentacin (ACPC) 294, transpentacin 295 & cishexacin (ACHC) 296

Due to the high demand for short and efficient asymmetric syntheses of these type of chiral building blocks it was decided to apply our cyclisation methodology to simple aliphatic ω-imino ester starting materials, with the aim of using it for the asymmetric synthesis of cispentacin and related analogues.

3.2 Synthetic Approaches to Cispentacin Derivatives

In the past decade interest in monocyclic β-amino acids has increased significantly with the first and most widely researched target being cispentacin **294**. Cispentacin (also referred to as *cis*-ACPC) exhibits potent antifungal activity and has found a broad range of applications including incorporation into β-peptides. In all cyclic β-amino acids, the carboxyl group is vicinal to the amine group, and consequently there are four possible stereoisomeric forms (Scheme 121).

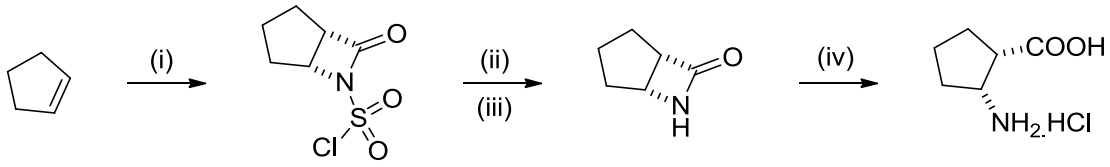


294a **294b** **295a** **295b**

Scheme 121- All four stereoisomers of ACPC

The ability to access all four stereoisomers of ACPC is a challenge that has been targeted by a number of synthetic groups. Access to enantiopure cispentacins is particularly important when incorporating them into β-peptides due to their ability to induce different folding properties. For example, transpentacin results in β-peptides that exhibit a 12-helical conformation[171] whereas cispentacin forms an extended strand type structure.[172]

Initially, a range of methods for the synthesis of racemic cispentacin were reported. The first synthesis of *rac*-cispentacin **300** was reported in 1972 by Nativ *et al*. They demonstrated that *rac*-cispentacin could be synthesised using a [2+2] cycloaddition reaction of chlorosulfonyl isocyanate with cyclopentene **297** to afford β-lactam **299**, followed by subsequent hydrolytic ring opening (Scheme 122).[173]



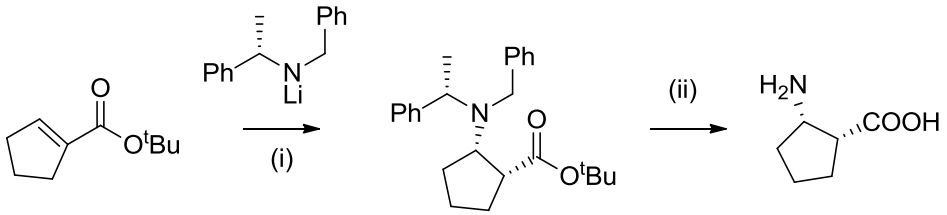
297 **(*rac*)-298** 46% Yield **(*rac*)-299** 45% Yield **(*rac*)-300** 45% Yield

Reagents & Conditions: (i) $ClSO_2NCO$; (ii) KI, $NaHSO_4$; (iii) NaOH, pH 7; (iv) conc. HCl, 3hrs

Scheme 122- Racemic synthesis of cispentacin *via* a [2+2] cycloaddition reaction[173]

Several other methods for the synthesis of racemic acyclic β-amino acids include protocols that rely on the selective reduction of enamines,[174-175] Diels-Alder reactions,[176] Michael additions to cycloalkanecarboxylic acids[177] and *via* 1,2-dicarboxylic acid rearrangements.[178] There are now a number of routes for producing enantiopure pentacin derivatives using asymmetric synthetic protocols, including strategies that employ the chiral pool, chiral auxiliaries, chiral catalysts or kinetic resolution.

Cispentacin **294** was first prepared in enantiopure form by Davies *et al.*[179] *via* conjugate addition of lithium (*S*)-(α-methylbenzyl)benzylamide to an α,β-unsaturated ester to afford (1*R*,2*S*)-cispentacin *tert*-butyl ester **302** in 98% *de* and 65% yield. Research by Davies *et al.* using chiral lithium salts to prepare both aliphatic and cyclic β-amino acids has continued to be developed and was the subject of a large review in 2005 (Scheme 123).[180]

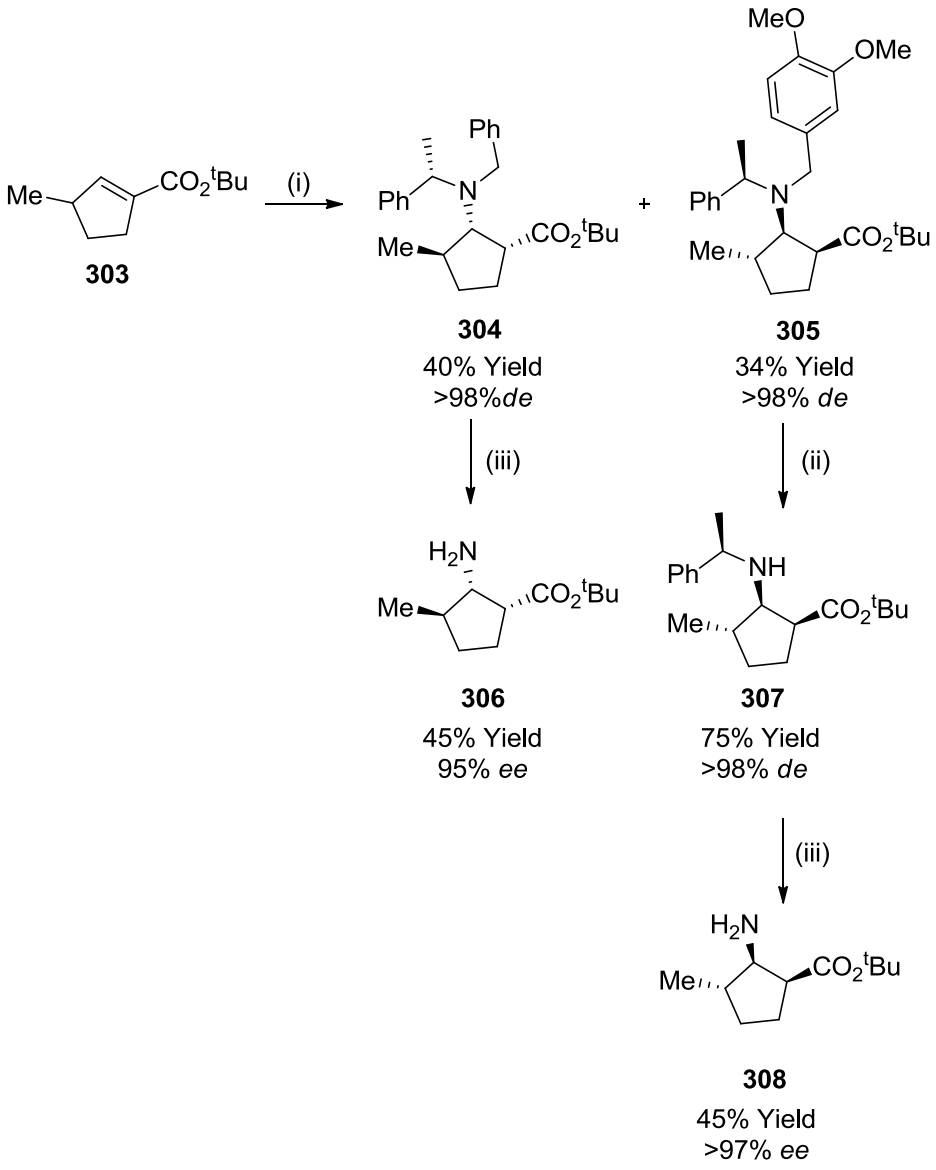


301 **302** 65% Yield >98% *de* **294** 72% Yield

Reagents & Conditions: (i) 2,6-Di-tert-butylphenol, THF; (ii) a) H_2, Pd/C, AcOH; b) HCl; c) Dowex 50XB-200

Scheme 123- Synthesis of (1*R*,2*S*)-Cispentacin using lithium (*S*)- *α*-methylbenzyl)benzylamide[179]

The initial work by Davies *et al.* on the asymmetric synthesis of cispentacin using enantiomerically pure lithium amides has continued to be developed for the synthesis of substituted cispentacin derivatives *via* parallel kinetic resolution.[181] In this case, treatment of (*rac*)-*tert*-butyl-cyclopentene-1-carboxylate with a mixture of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl) amide results in enantiorecognition *via* a mutual kinetic resolution process, to give the enantiomeric addition products **306** and **308**. This kinetic resolution enables the synthesis of a variety of C3-alkyl substituted cispentacin derivatives. In addition, epimerisation of the carboxylate centre enables access to alkyl substituted transpentacin derivatives[182] which have since been successfully incorporated into β-peptides (Scheme 124).[183]

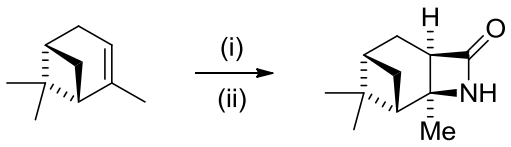


Reagents & Conditions: (i) Lithium (S)-N-benzyl-N(α-methylbenzyl)amide, lithium (R)-N-3,4-dimethoxybenzyl-N-(α-methylbenzyl)amide (50:50), 2,6-di-tert-butylphenol THF, -78°C, 3hrs; (ii) DDQ, DCM:H_2O (3:1); (iii) $Pd(OH)_2$/C, MeOH, H_2, (5 atm), rt

Scheme 124- Synthesis of γ-alkyl substituted cispentacin[181]

Since the initial asymmetric synthesis of cispentacin in 1993, a number of new methods have been developed for the synthesis of chiral monocyclic β-amino acids. One approach involves utilization of the chiral pool for the synthesis of a substituted cishexacin β-lactam from (+)-α-pinene **309** (Scheme 125),[184] whilst another example

involves the use of a D-glucose derivative to access polyhydroxylated transpentacins (Scheme 126).[185]

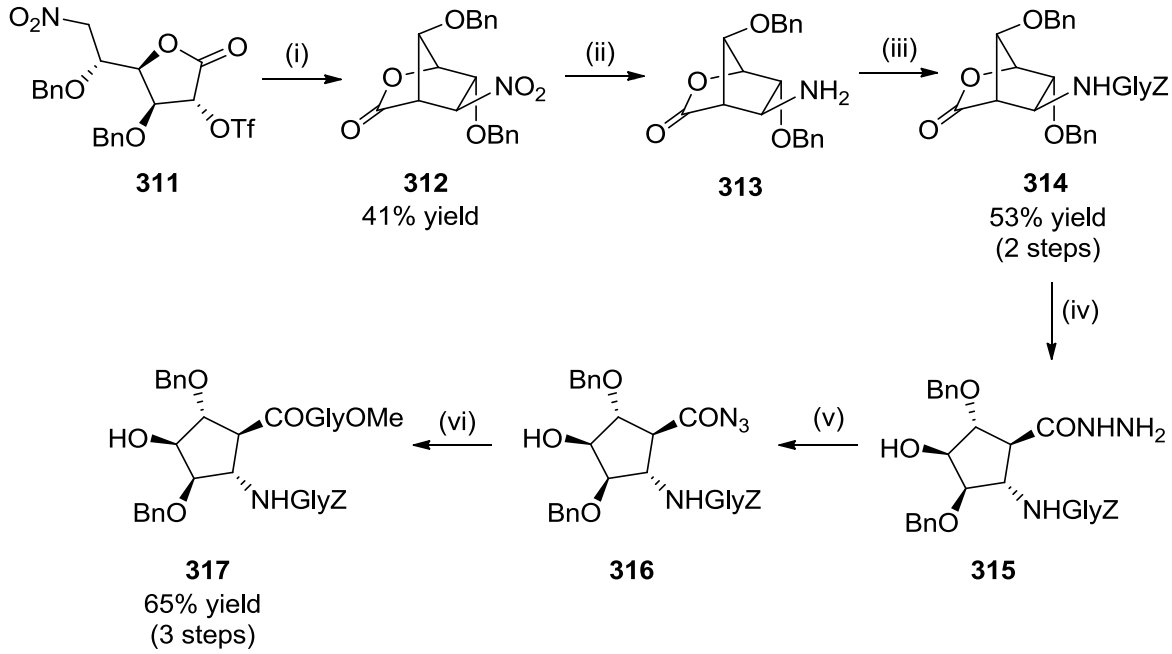


309 **310** 76%

Reagents & Conditions: (i) CSI, 1hr, rt; (ii) KOH, Na_2SO_3

Scheme 125- Synthesis of cishexacin β-lactam using (+)-α-pinene

The key steps in the formation of polyhydroxylated transpentacins involve the peptide coupling of lactone **313** with benzyloxycarbonylglycine, ethyl chloroformate and triethylamine to give the dipeptide **314** and the subsequent ring opening reaction using hydrazine to give the protected D-glucose derivative **315**.



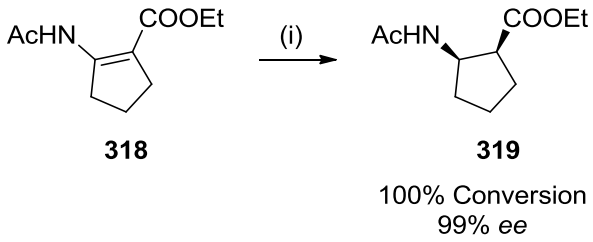
311 **312** 41% yield **313** **314** 53% yield (2 steps) **315** **316** **317** 65% yield (3 steps)

Reagents & Conditions: (i) TBAF, THF; (ii) H_2, Raney-Ni, MeOH; (iii) $ClCO_2Et$, Z-Gly, Et_3N, (iv) H_2NNH_2, MeOH; (v) t-$BuNO_2$, HCl, DMF, dioxane; (vi) Gly-CO_2Me, Et_3N, DMF

Scheme 126- Synthesis of substituted transpentacin from a derivative of D-glucose[185]

Although these examples show how the chiral pool can be used to provide access to some monocyclic β-amino acids, this type of methodology has several drawbacks such as long synthetic routes, high expense and the configuration of the product being limited to the availability of naturally occurring chiral starting materials.

The catalytic reduction of enamines to afford β-amino acids has been well documented[103] with the first asymmetric synthesis of monocyclic β-amino ester *via* enantioselective reduction of an enamine using a chiral ruthenium catalyst being reported in 2003 (Scheme 127).[186] Zhang *et al*. reported that *N*-acyl-β-amino ester **319** could be produced in 99% *ee* and 100% conversion using (*S*)-BINAP as a chiral ligand, with a variety of other chiral ligands having also been investigated.[186] The use of this chiral ruthenium catalyst provides an excellent way of converting a prochiral β-amino ester into an enantiopure *cis*-β-amino ester, with the corresponding transpentacin being obtained by epimerization.[186]



318 **319**

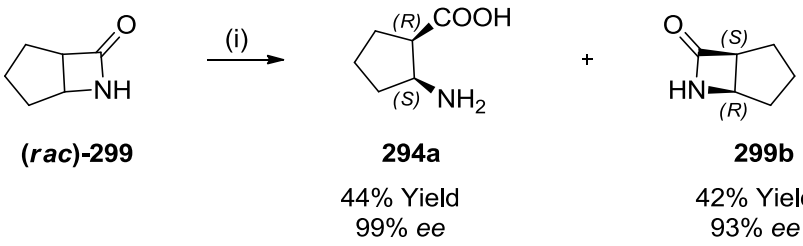
100% Conversion
99% *ee*

Reagents & Conditions: (i) Ru(COD)(Methallyl)$_2$, (S)-BINAP, HBF$_4$, H$_2$, MeOH, rt

Scheme 127-Enantioselective hydrogenation reaction to form a β-amino ester[186]

The stereoselective synthesis of β-amino acid derivatives using enzymatic kinetic resolution is well documented and such methods have been investigated extensively.[115,124,126,187-189] In 2003, Fulop *et al.* devised an efficient and simple methodology for the lipase-catalysed enantioselective ring opening of alicyclic fused β-lactams.[190] This enantioselective ring opening reaction furnished enantiopure (1*R*,2*S*)-cispentacin and the corresponding (1*S*,5*R*)-β-lactam in high yield and excellent *ee* that could be easily separated. The (1*S*,5*R*)-β-lactam was subsequently ring opened using acid hydrolysis to obtain the other cispentacin enantiomer. This enzymatic methodology has recently been employed for the synthesis of fluorinated alicyclic β-amino esters[191] and key intermediates for the Taxol side chain.[192] Therefore, while the significance of

this enzymatic process has been established, the main drawbacks of this approach are the substrate specific nature of the enzymes employed (Scheme 128).



(*rac*)-299 **294a** **299b**

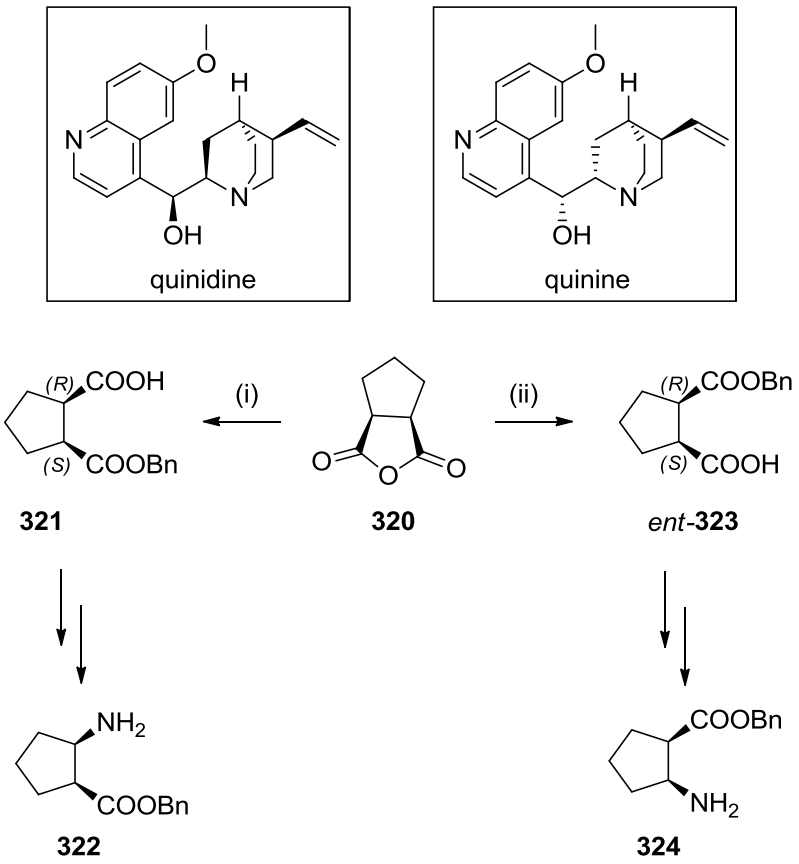
44% Yield
99% *ee*

42% Yield
93% *ee*

Reagents & Conditions: (i) H_2O, Lipolase, i-Pr_2O, 60 °C

Scheme 128- Enantioselective ring opening of an alicyclic β-lactam[190]

In 2003, desymmeterisation of *meso*-anhydrides was achieved using either quinidine or quinine as nucleophilic catalysts to mediate the addition of benzyl alcohol to give mono benzyl esters **322** or **324**. Subsequent Curtius degradation of these monobenzyl ester acids afforded the corresponding benzyl cispentacin esters in high *ee*.[193] The (*S*)-benzyl hemiester can be obtained using a quinidine mediated desymmetrisation, whereas the (*R*)-benzyl hemiester can be generated using a quinine additive. This allows access to either cispentacin enantiomer in up to 97% *ee* and 93% yield (Scheme 129).[193]



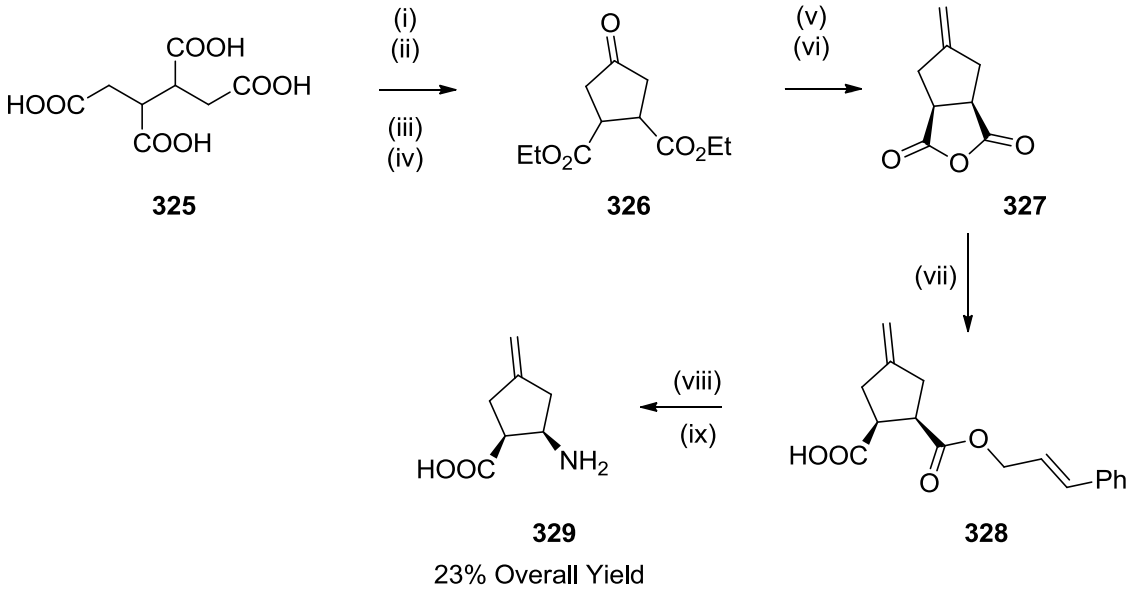
Reagents & Conditions: (i) Quinidine (1.1 equiv.), benzyl alcohol (3.0 equiv.), toluene, -55°C; (ii) Quinine (1.1 equiv.), benzyl alcohol (3.0 equiv.), toluene, -55°C

Scheme 129- Synthesis of cispentacin *via* desymmetrisation of a *meso*-anhydride

More recently a quinine-mediated parallel kinetic resolution has been used to synthesise the antifungal Icofungipen. Icofungipen, also referred to as BAY 10-888, has a dual mode of action as a novel antifungal and is currently in phase II clinical studies as a treatment for yeast infections.[194] For example, Mittendorf *et al*. have developed a synthesis that enables (1*R*,2*S*)-Icofungipen **239** to be prepared on a multi-kilogram scale.[195]

As illustrated in Scheme 130 the substituted cyclopentanone diester **326** is synthesised from tetra-acid **325** using a Dieckmann cyclisation followed by acid catalysed decarboxylation and esterification with ethanol. The alkene functionality is installed using a methylene Wittig reaction and the dicarboxylic acid is converted into *meso*-anhydride **327**. A quinine mediated alcoholysis of the anhydride **327** was carried out using *trans*-cinnamyl alcohol, which generated the enantiomer **328** in >99% *ee*. Lastly,

a Curtius rearrangement furnished the protected β-amino ester, which was subsequently deprotected to give (1*R*,2*S*)-Icofungipen **329** in an overall 23% yield (Scheme 130).[195]



325 **326** **327** **328** **329**

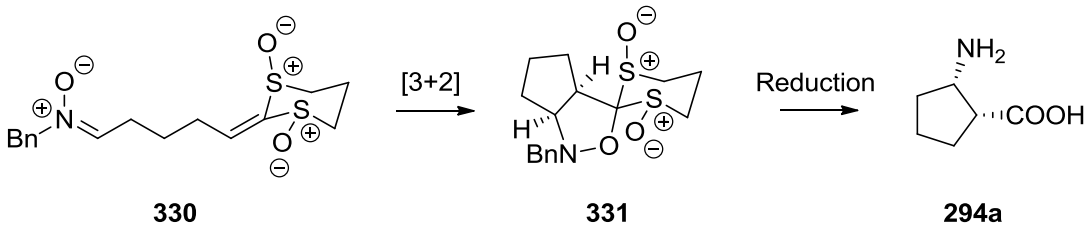
23% Overall Yield

Reagents & Conditions: (i) EtOH, H_2SO_4; (ii) NaOMe, MeOH; (iii) HCl, H_2O; (iv) EtOH, H_2SO_4; (v) $Ph_3PMe^+Br^-$, t-BuOK, THF then KOH, THF; (vi) $(EtCO)_2O$, 135°C; (vii) Quinine, (2E)-3-phenyl-2-propane-1-ol, toluene, -15°C; (viii) $(PhO)_2PON_3$, NEt_3, toluene, then (2E)-3-phenyl-2-propane-1-ol reflux; (xi) $Pd(OAc)_2$, PPh_3, morpholine, EtOH

Scheme 130- Quinine mediated synthesis of (1*R*,2*S*)-Icofungipen 329[195]

Research in this area continues and more recently in 2007 all four enantiomerically pure isomers of Icofungipen **329** have been synthesised using a quinine-mediated parallel kinetic resolution protocol.[196]

Another asymmetric process for the synthesis of cispentacin involves an intramolecular nitrone cycloaddition onto a C_2-symmetric ketene bis-sulfoxide.[197] The facial selectivity of the [3+2] cycloaddition reaction of the nitrone **330** onto the alkene functionality is controlled by diastereoselective steric interactions that occur within the transition state. This results in a defined tricyclic product that was subsequently reduced to form (1*R*,2*S*)-cispentacin **294a**. More recently this methodology has been utilized to generate the cispentacin analogue cis-(3*R*,4*R*)-4-amino-pyrrolidine-3-carboxylic acid (Scheme 131).[198]



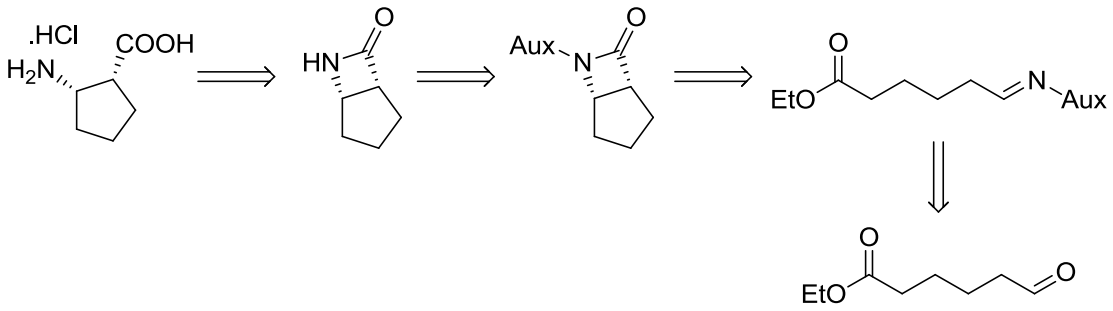
330 **331** **294a**

Scheme 131- Intramolecular nitrone cycloaddition for the asymmetric synthesis of cispentacin[197]

In summary, there are a number of methodologies that have been devised in order to prepare enantiopure cispentacin analogues, including the use of chiral catalysts, kinetic resolutions, intramolecular nitrone cycloadditions as well as lithium amide conjugate additions. Despite attempts at functionalisation of the cispentacin ring, many of these methodologies are substrate specific and as such only give access to a limited range of derivatives. Therefore, it was the aim of the research described in this chapter to employ our *intramolecular* enolate-imine cyclisation methodology for the efficient asymmetric synthesis of cispentacin, as well as some of its analogues.

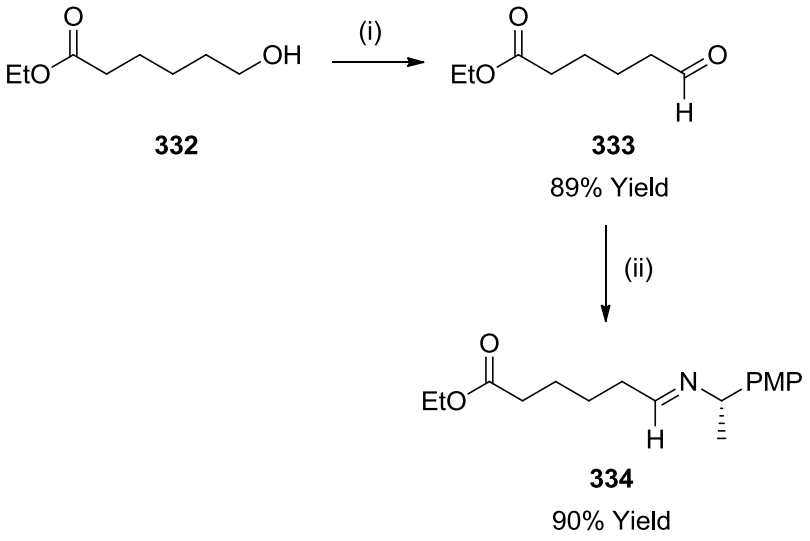
3.3 Chiral Imino Ester Synthesis

The aim of employing an intramolecular enolate-imine cyclisation reaction to generate cispentacin in high yields and diastereoselectivity required a simpler synthetic route compared with that used for the synthesis of the benzocispentacin substrates. The proposed retrosynthesis shown in Scheme 132 reveals that the asymmetric synthesis of cispentacin could potentially be prepared using a short and potentially high yielding methodology.



Scheme 132- Retrosynthesis of cispentacin

In devising the cheapest and most efficient synthetic route, it was found that ethyl 6-hydroxyhexanoate **332** was commercially available. Its alcohol fragment was easily oxidised to its corresponding aldehyde, using pyridinium chlorochromate (PCC) to afford ethyl 6-oxohexanoate **333** in 89% yield (Scheme 133).

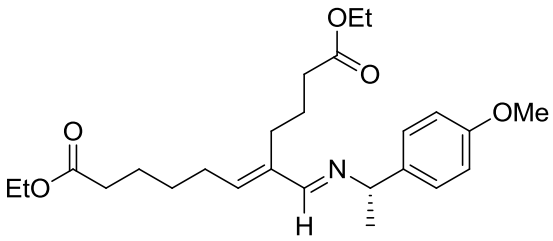


Reagents & Conditions: (i) PCC, DCM; (ii) (S)-α-methyl-p-methoxybenzylamine, $MgSO_4$, DCM, 2hrs

Scheme 133- Synthesis of (*S*,*E*)-ethyl 6-((1-(4-methoxyphenyl)ethyl)imino)hexanoate

The chiral imine **334** was formed in a 90% yield *via* treatment of aldehyde **333** with (*S*)-α-methyl-*p*-methoxybenzylamine with its formation being established by the presence of an imine proton as a triplet at 7.71 ppm in the ^{1}H NMR spectrum of the crude reaction product.

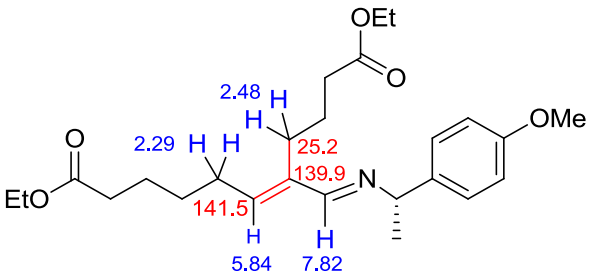
The initial imine reaction was reanalyzed after a few hours, which revealed the emergence of an impurity over time. In fact after 48 hours there was none of the original imine **334** left in the reaction, with only a new imine product present, as well as residual amine in a 1:1 ratio. This observation required further investigation as it was important to understand what effect the formation of this new imine might have on the overall success of the enolate-imine cyclisation reaction. The unknown impurity was subjected to a series of 1D and 2D NMR experiments with the ^{1}H, ^{13}C, COSY, HSQC and HMBC spectra (Appendix 5.1 - 5.2) enabling the structure of the dimeric imine **335** to be determined (Figure 31).



335

Figure 31- Proposed structure of impurity 335

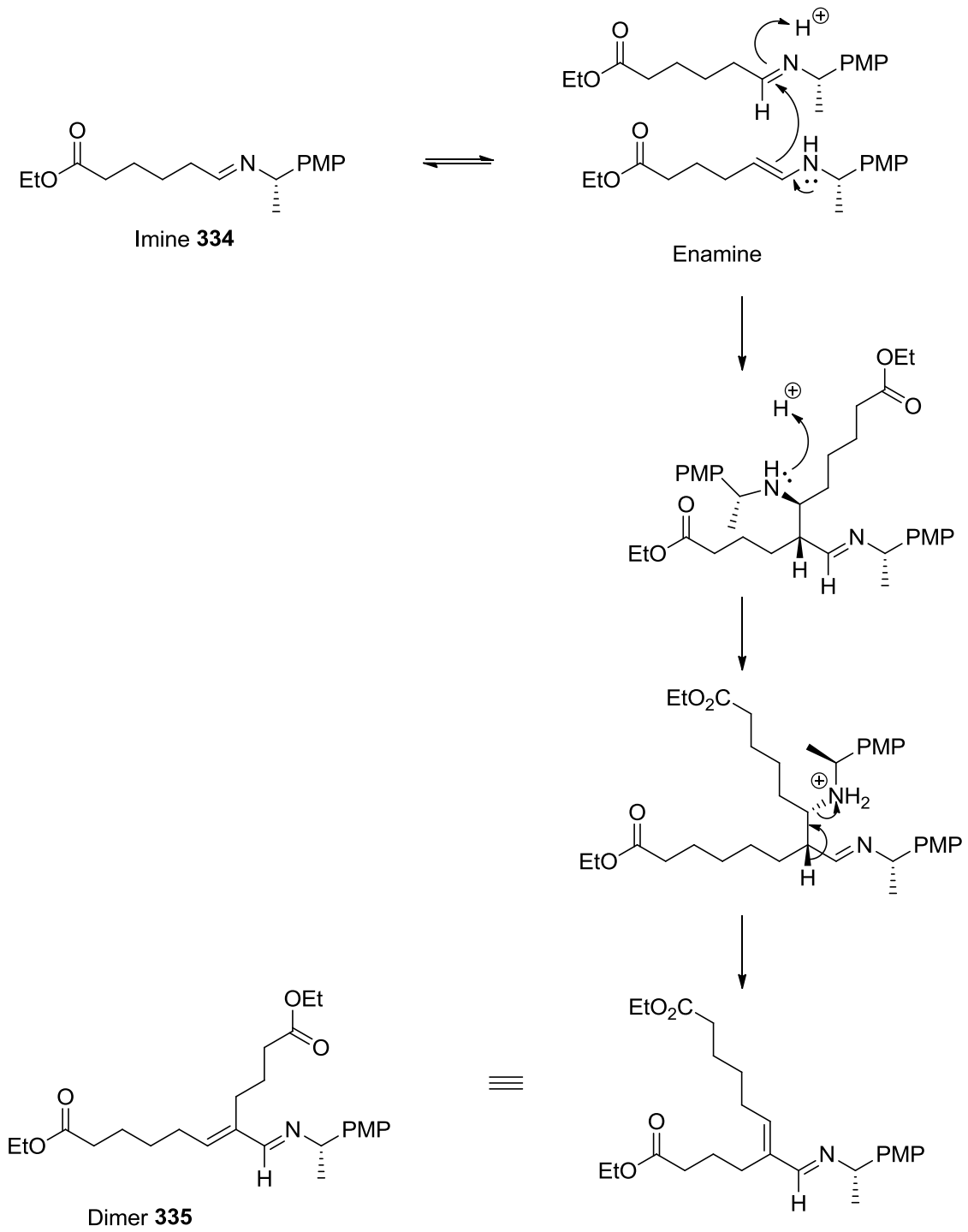
The key correlations in the HMBC spectrum which helped in the identification of **335** showed that the imine proton (7.82 ppm) of this "imine dimer" was interacting with the carbon atoms of the adjacent double bond (139.9 ppm and 141.5 ppm), as well as to a methylene group at 25.2 ppm. The (*E*)-geometry of the double bond was confirmed using the NOESY spectrum which reported correlation between the protons at 2.48 ppm and 2.29 ppm, and another correlation between the imine proton at 7.82 ppm and the alkene proton at 5.84 ppm. Furthermore, the high resolution mass spectrometry data reported a clean and well defined m/z value of 432.2744 consistent with the formation of a dimer **335** (Figure 32).



335

Figure 32- Correlations observed in HMBC spectrum of 335

A mechanism for the proposed formation of dimer **335** is shown in Scheme 134. Initially, (*S*,*E*)-ethyl 6-((1-(4-methoxyphenyl)ethyl)imino)hexanoate **334** is in equilibrium with its enamine tautomer, this enamine attacks a second equivalent of the imine **334** resulting in the formation of a dimer. The amino group is then protonated and undergoes an E2-elimination reaction to form imine-diene, thus releasing α-methyl *p*-methoxybenzylamine.



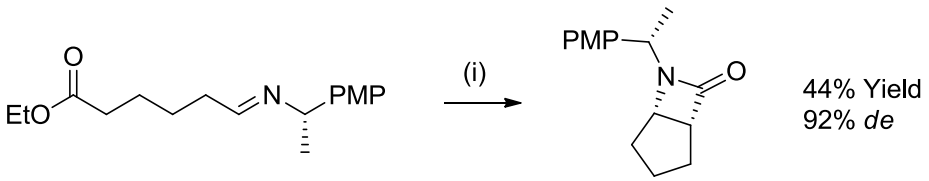
Scheme 134- Proposed mechanism for formation of dimer 335

In summary, the chiral imino ester (*S*,*E*)-ethyl 6-((1-(4-methoxyphenyl)ethyl)imino) hexanoate **334** which was required as a starting material for the enolate-imine cyclisation reaction could be prepared and isolated. However, this chiral imino ester

334 proved to be very unstable, with dimerisation occuring readily to form a conjugated imine substrate **335**. This fact would need to be taken into account when attempting subsequent cyclisation reactions.

3.4 Cispentacin Cyclisation and Optimisation

The intramolecular enolate-imine cyclisation methodology was then tested on (*S*,*E*)-ethyl 6-((1-(4-methoxyphenyl)ethyl)imino)hexanoate **334**. Initial reactions were carried out using the optimized conditions developed for benzocispentacin, with the exception that the reactions were carried out at room temperature. As seen previously, carrying out the cyclisation reaction at room temperature should result in a lower *de*, but was predicted to maximise the yield of **336**, thus enabling confirmation that the enolate-imine cyclisation was viable for this substrate. Using these initial conditions the protected β-lactam **336** was isolated in 44% yield and 92% *de*. The success of this reaction was determined by the presence of a diagnostic peak at 3.32 ppm in its ^{1}H NMR spectrum (seen in Appendix 5.1). Further to this, the *de* could be determined by comparing the two sets of quartets from the chiral auxiliary in the major and minor diastereomers; observed at 4.81 ppm for the major diastereomer, and at 4.70 ppm for the minor diastereomer fragments (Scheme 135).



334 **336**

Reagents & Conditions: (i) NaHMDS (2.0 equiv), 15-crown-5, THF, rt, 18 hrs.

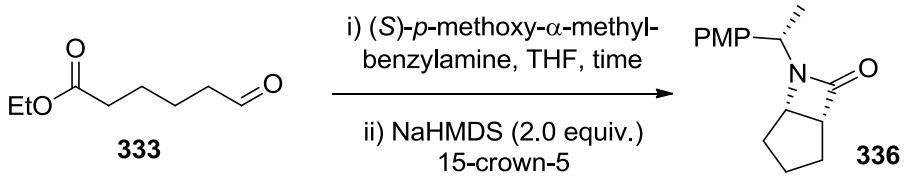
Scheme 135- Initial cyclisation reaction of (*S,E*)-ethyl 6-((1-(4-methoxyphenyl)ethyl)imino)-hexanoate 334

The next step was to optimise the reaction in order to increase the yield for formation of the (*S*,1*R*,2*S*)-β-lactam **336**. It was decided that due to its instability, it might be beneficial to form imine **334** *in situ* so that there would insufficient time for dimerisation to take place. In light of this, it was decided to carry out the imine formation in THF

rather than DCM, with molecular sieves added to remove any water produced during the imine formation.

As can be seen in Table 13, the length of time employed for formation of the imine *in situ* has a marked affect on the isolated yield of the β-lactam product **336**. To summarise, if imine **334** is isolated and left for any length of time it distinctly reduces the yield of β-lactam **336** (Table 13, Entries 1 and 2), which is to be expected as once the imine has dimerised it is no longer able to cyclise. Upon further inspection it became clear that imine formation was extremely rapid resulting in complete consumption of aldehyde **333** in less than 10 minutes. Therefore, as confirmed by Entry 4, imine **334** can be generated *in situ* and the cyclisation reaction carried out after 10 minutes *via* addition of NaHMDS and 15-crown-5 ether, which gave a much improved yield of β-lactam **336** of 64% and a good 92% *de*.

Table 13- Effect of imine 334 formation

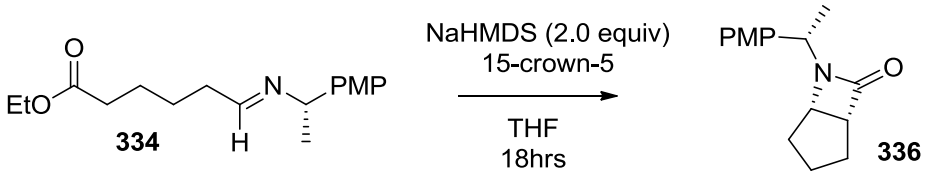


Entry	Imine Formation	Isolated Yield (%)	*de* (%)
1	Stored- 96 hours	24	92
2	Stored- 2 hours	44	92
3	*Insitu* – 45 mins	63	92
4	*Insitu* – 10 mins	64	92

The second variable addressed was the temperature of the reaction, since previous results had shown that lower temperatures could improve the *de* of these types of cyclisation reactions. The cyclisation reaction was attempted at a range of lower temperatures in order to find the highest *de*, and in addition, the effect of refluxing the

reaction was also investigated. As predicted, lowering the temperature improved the *de* but at the same time resulted in a decrease in yield. In terms of stereoselectivity, carrying out the cyclisation reaction at -45 °C and allowing it to warm to room temperature gave *N*-aryl-β-lactam **336** in 50% yield and 98% *de* (Table 14, Entry 3). Interestingly, when the reaction was attempted at reflux (entry 5) the yield was lower than at room temperature, but there was also a significant decrease in the diastereoselectivity, potentially due to competing formation of a thermodynamic (*Z*)-enolate (Table 14, Entry 5).

Table 14- Effect of temperature on cyclisation reaction

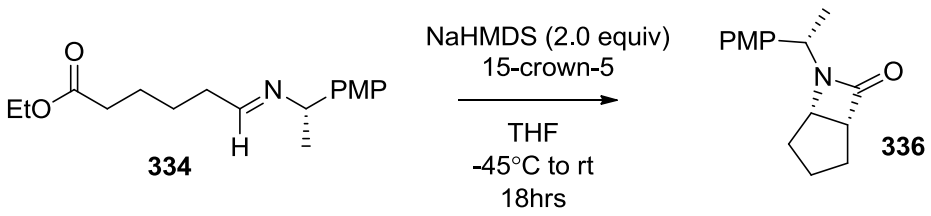


Entry	Temp (°C)	Isolated Yield (%)	*de* (%)
1	rt	64	92
2	0 to rt	57	94
3	-45 to rt	50	98
4	-78 to rt	26	99
5	Reflux	41	82

A factor not previously investigated was the concentration of the cyclisation substrate, as prior experiments had previously been carried out at a standard concentration of 0.05 M. Consequently, the effect of increasing and decreasing the concentration of the substrate was examined since this had the potential to reduce potential oligomerisation pathways and minimize the amount of imine **325** produced from the unwanted enamine-imine dimerisation pathway. Increasing the substrate concentration to 0.5 M resulted in a much lower yield with the *de* only affected slightly. By increasing the substrate concentration the chance of competing intermolecular enolate-imine

oligomerisation reactions and/or imine dimerisation reactions increases, resulting in unwanted products of polymerisation or dimerisation. In comparison, decreasing the substrate concentration to 0.005 M also gave an extremely poor yield and lowered the *de* to 81%. This reaction required a large amount of solvent and it was very difficult to uniformly maintain -45 °C throughout the reaction flask which may have resulted in the lower *de*. Therefore, our original concentration of 0.05 M for carrying out these cyclisation reactions was deemed optimal.

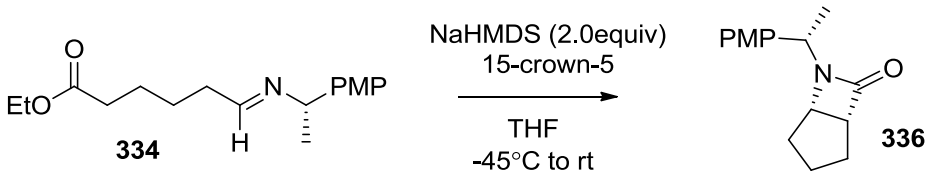
Table 15- Effect of the substrate concentration on cyclisation reaction



Entry	Substrate Conc (M)	Isolated Yield (%)	*de* (%)
1	0.05	50	98
2	0.5	15	99
3	0.005	4	81

In order to obtain the highest yield the reaction had previously been left overnight for 18 hours, but to improve the efficiency of the overall synthesis the optimum reaction time was explored. As can be seen from Entry 2 the cyclisation reaction gave identical results after 6 hours to those obtained after 18 hours - giving a slightly higher yield and a 99% *de*. However, if the reaction time was decreased further to only 1 hour the cyclisation reaction was found not to have proceeded to completion and therefore the yield was lower.

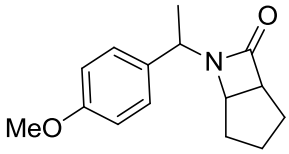
Table 16- Effect of reaction time on the cyclisation reaction



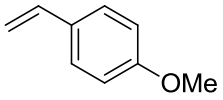
Entry	Time (hrs)	Isolated Yield (%)	*de* (%)
1	18	50	98
2	6	52	99
3	1	38	99

The highest yield of β-lactam **336** observed in the optimization process was 64%, but this posed the question of where the rest of the starting material **334** was going? When the crude product was isolated after work up (using NH_4Cl and water) only the β-lactam **336** was observed in the ^1H NMR spectrum. Occasionally a small amount of starting material could be seen in the ^1H NMR depending on the conditions. In contrast to the benzocispentacin substrates (Scheme 101), none of the corresponding β-amino esters were ever observed.

In order to determine what was happening to the rest of the starting material the reaction was monitored directly by LCMS. A sample from the reaction mixture was taken at 1 and 6 hours to identify what components were present in solution. The two main components in the LCMS traces had an m/z value of 246 and 135, corresponding to the β-lactam **336** and a fragment of free amine **337** respectively (Figure 33). This suggests that either the imine **334** is unstable and adventitious water can convert back into its parent aldehyde and amine, or that excess base may be causing E2-elimination of the chiral auxiliary fragment of the β-lactam product. Furthermore, the high resolution mass spectrometry data for the dimer **325**, also revealed peaks at 135.08, supporting the theory that the imine **334** was dimerising during the reaction.



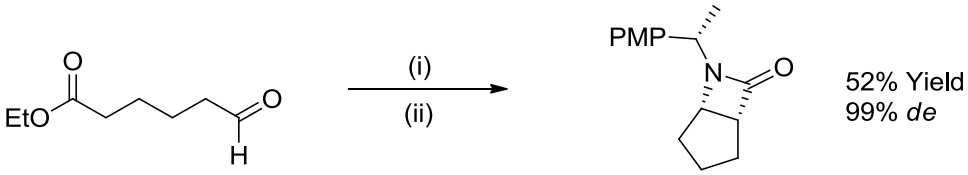
336
Formula: $C_{15}H_{19}NO_2$
Exact Mass: 245.14
$[M+H]^+$: 246.14



337
Formula: $C_9H_{10}O$
Exact Mass: 134.07
$[M+H]^+$:135.08

Figure 33- Fragments observed in LCMS analysis

Therefore, based upon the data collected, the optimal reaction conditions required the imine to be generated *in situ* at room temperature for 10 minutes, the reaction then cooled to -45 °C, before NaHMDS and 15-crown-5 were added to initiate enolate cyclisation. This enabled ethyl-6-oxohexanoate **333** to be converted into the (*S*,α*R*,β*S*)-β-lactam of cispentacin in 52% isolated yield after purification by chromatography.



333 **336**

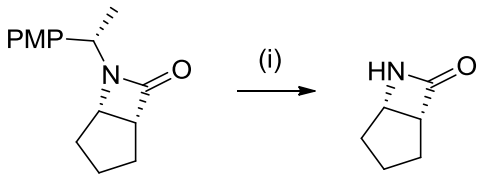
Reagents & Conditions: (i) (S)-α-Methyl-p-methoxybenzylamine, $MgSO_4$, THF, rt, 10 mins; (ii) NaHMDS (2.0 equiv.), 15-Crown-5, THF, -45°C to rt, 6 hrs.

Scheme 136- Synthesis of (1*R*,5*S*)-6-((*S*)-1-(4-methoxyphenyl)ethyl)-6-azabicyclo[3.2.0]heptan-7-one

3.5 Synthesis of Cispentacin and Transpentacin Ethyl Ester

Having developed a successful synthesis of (1*R*,5*S*)-6-((*S*)-1-(4-methoxyphenyl)ethyl)-6-azabicyclo[3.2.0]heptan-7-one **336**, the next stage was to deprotect it to its corresponding β-amino acid and β-amino ester for use as foldamer monomers. The first step was removal of the chiral auxiliary using the previously described CAN mediated conditions.[149] The deprotected β-lactam (1*R*,5*S*)-6-azabicyclo[3.2.0]heptan-7-one **338** was isolated as a white solid in 71% yield (Scheme 137). The configuration of the (*S*,α*R*,β*S*)-β-lactam **338** was confirmed by comparing its specific rotation value of

$[a]_D^{17}$ -33.3 (c 0.87, $CHCl_3$) to the reported literature value of $[a]_D^{25}$ -35.9 (c 0.5, $CHCl_3$).[190]

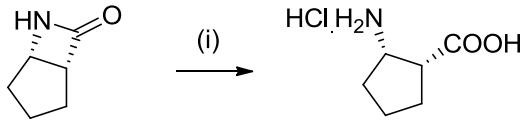


336 **338**
71% Yield

Reagents & Conditions: (i) CAN (4.0 equiv), MeCN-H_2O (1:1), rt, 4 hrs

Scheme 137- Deprotection of (1*R*,5*S*)-6-((*S*)-1-(4-methoxyphenyl)ethyl)-6-azabicyclo[3.2.0]heptan-7-one 338

The hydrochloride salt of the corresponding β-amino acid **300a** (cispentacin) was then prepared by acidic hydrolysis of (1*R*,5*S*)-6-azabicyclo[3.2.0]heptan-7-one **338** in 97% yield (Scheme 138). A specific rotation of $[\propto]_D^{19}$ -5.0 (*c* 0.5, H_2O) was obtained for β-amino acid **300a**, which compares favourably with the literature value of $[a]_D^{25}$ -5.1 (c 0.5, H_2O).[190]

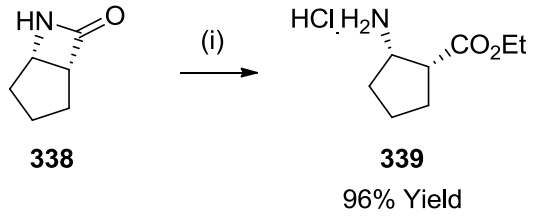


338 **300a**
97% Yield

Reagents & Conditions: (i) 18% HCl, reflux, 3 hrs

Scheme 138- Synthesis of (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid hydrochloride 300a

Alternatively, the hydrochloride salt of *cis*-β-amino ethyl ester **339** could also be synthesised by ring opening of the β-lactam **338** in the presence of ethanol in 96% yield (Scheme 139). The (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid ethyl ester **339** has been employed for the synthesis of a promising polymerase inhibitor.[199] The literature method requires recrystallisation of the selected enantiomer resulting in a low overall yield of 29%,[199] compared with the 35% overall yield using our methodology.



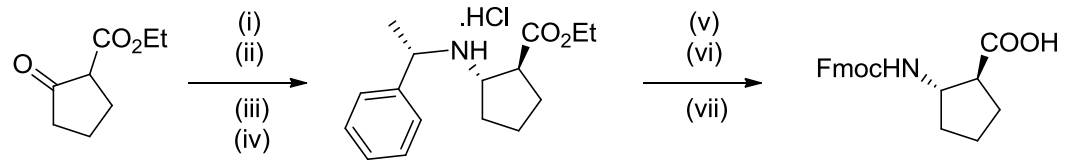
338 **339**

96% Yield

Reagents & Conditions: HCl (1M in Et_2O), EtOH, reflux, 3 hrs

Scheme 139- Synthesis of (1*R*,2*S*)-ethyl 2-aminocyclopentanecarboxylate hydrochloride 339

Another target for our methodology was the synthesis of transpentacin. Gellman *et al*. have reported that transpentacin is one of the most competent subunits for the formation of helical foldamers.[105] In 2001, they reported that reductive amination of a β-ketoester could be used to form the (α*S*,β*S*) β-amino ester salt **341** using (*S*)-α-methylbenzylamine in a 29% overall yield.[200] Following this, the (α*S*,β*S*)-β-amino ester salt **341** was subjected to reductive removal of the auxiliary, saponification and protection with Fmoc.[200] This produced the *trans*-Fmoc-ACPC residue **342** in an 85% yield which was a useful building block for the solid phase synthesis of β-peptides (Scheme 140).[200]



340 **341** **342**

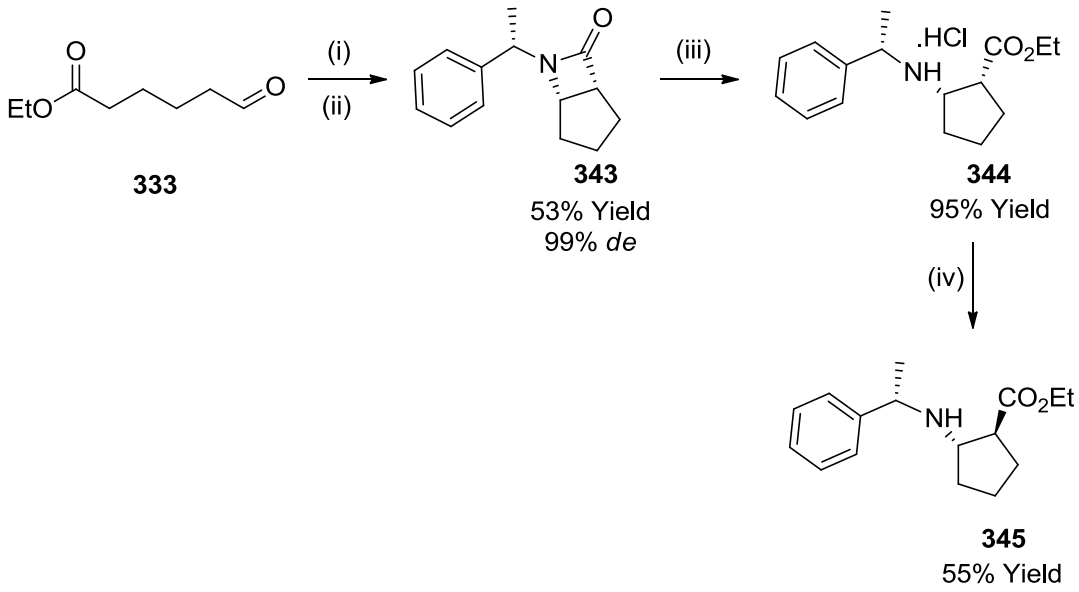
29% Yield 85% Yield

Reagents & Conditions: (i) (S)-α-Methylbenzylamine; (ii) $NaBH_3CN$; (iii) HCl; (iv) Recrystallisation; (v) $LiOH.H_2O$; (vi) H_2, 10% Pd/C; (vii) Fmoc-OSu

Scheme 140- Synthesis of *trans*-Fmoc-ACPC 342[200]

Therefore, it was decided that our intramolecular enolate-imine cyclisation protocol would be expanded in an attempt to produce a more efficient synthesis of a precursor to the *trans*-Fmoc-ACPC residue **342**. The synthesis was modified to use (*S*)-α-methylbenzylamine as a chiral auxiliary to allow for its subsequent removal by hydrogenation as shown in Scheme 141.

The required imine was generated *in situ*, which was followed by the enolate cyclisation step to give the β-lactam **343** in 53% yield and 99% *de*. This β-lactam **343** was subsequently ring opened to form the *cis*-β-amino ester salt **344** in 95% yield. The final step involved epimerization of the ester group to give (α*S*,β*S*)-β-amino ester **345**, giving diastereotopic protons that correlated to those reported by Gellman *et al.,*[200] this produced the (1*S*,2*S*)-ethyl 2-(((*S*)-1-phenylethyl)amino)cyclopentanecarboxylate **345** in an overall yield of 28%, with this derivative having previously been converted into the Fmoc-derivative **342**.[200]



333

343
53% Yield
99% *de*

344
95% Yield

345
55% Yield

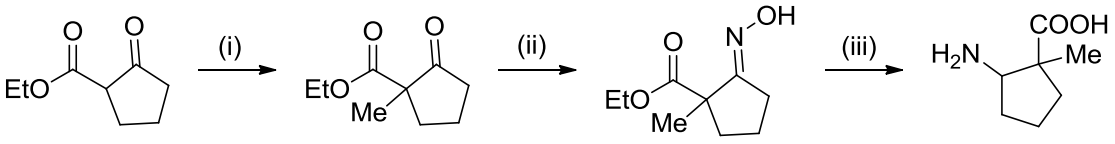
Reagents & Conditions: (i) (S)-α-Methylbenzylamine, THF, rt, 10 mins; (ii) NaHMDS, 15-Crown-5, THF, -45 °C to rt, 6 hrs; (iii) HCl, EtOH, reflux, 3 hrs; (iv) KO^{t}Bu, EtOH, reflux, 4 hrs

Scheme 141- Synthesis of (1*S*,2*S*)-ethyl 2-(((*S*)-1-phenylethyl)amino)cyclopentanecarboxylate

These results provide evidence that (1*R*,5*S*)-6-((*S*)-1-(4-methoxyphenyl)ethyl)-6-azabicyclo[3.2.0]heptan-7-one **345** can be rapidly prepared using our intramolecular enolate-imine cyclisation methodology, thus enabling access to a range of useful scaffolds for β-peptide foldamer formation.

3.6 Attempted Synthesis of α–Methyl-Substituted Cispentacin Synthesis

Another desirable building block for β-peptide formation would be (1*R*,2*S*)-2-amino-1-methylcyclopentanecarboxylic acid **349** which contains a quaternary α-stereocentre. A search of the literature showed that the synthesis of the racemate of 2-amino-1-methylcyclopentanecarboxylic acid was reported in 1983, based on the selective reduction of an oxime (Scheme 142).[201] Therefore our methodology could potentially afford the first asymmetric synthesis of this α,α-disubstituted β-amino acid **349**.

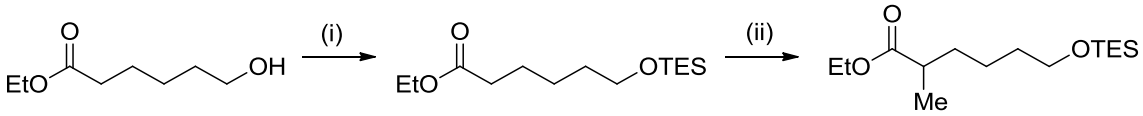


346 **347** **348** **349**

Reagents & Conditions: (i) a) KOH, ethanol; b) methyl iodide, toluene, 6 hrs, reflux; (ii) $HONH_2$.HCl, KOH, ethanol; (iii) NaOH, ethanol, 1hr, reflux

Scheme 142- Racemic synthesis of β-amino acid target containing a quaternary α-centre[201]

The cheap and readily available ethyl 6-hydroxyhexanoate **332** was chosen as the starting material and in its alcohol functionality would need to be protected as a silyl group. Consequently, treatment of **332** with TES-triflate and 2,6-lutidine in DCM was used to form the TES-protected alcohol **350** in 77% yield. In order to introduce the methyl substituent, the ester enolate was generated using NaHMDS in THF at -78 °C, followed by alkylation with methyl iodide to afford (*rac*)-ethyl ester **351** in 65% yield (Scheme 143).

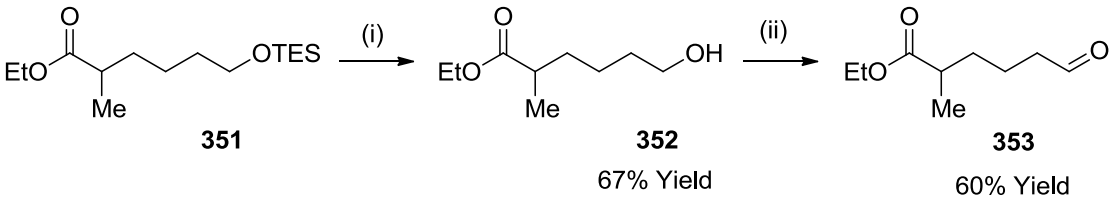


332 **350** 77% Yield **351** 65% Yield

Reagents & Conditions: (i) TES-triflate, 2,6-lutidine, DCM; (ii) NaHMDS, methyl iodide, THF, -78°C

Scheme 143- α-Alkylation of ethyl 6-hydroxyhexanoate

The triethylsilyl group of **351** was then removed using TBAF to give ethyl 6-hydroxy-2-methylhexanoate **352** in 67% yield, whose alcohol group was then oxidized *via* treatment with PCC in DCM to give ethyl 2-methyl-6-oxohexanoate **353** in 60% yield (Scheme 144).

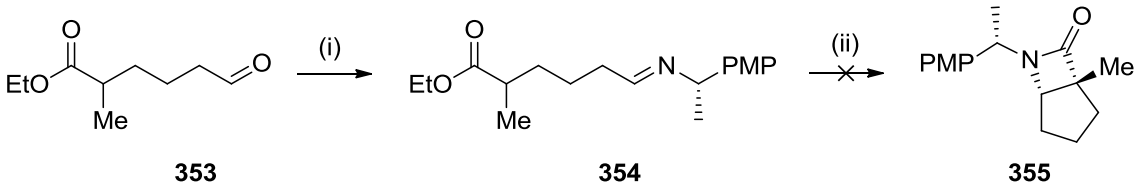


351 **352** 67% Yield **353** 60% Yield

Reagents & Conditions: (i) TBAF, THF; (ii) PCC, DCM

Scheme 144- Synthesis of ethyl 2-methyl-6-oxohexanoate 353

Due to the previously reported problem with the dimerisation of imine **334** it was decided to generate ethyl 6-(((*S*)-1-(4-methoxyphenyl)ethyl)imino)-2-methylhexanoate **354** *in situ*, with the progress of the reaction being monitored by TLC to ensure complete imine formation. Imine formation was complete after 1 hour and the cyclisation reaction was attempted *via* addition of NaHMDS and 15-crown-5 at room temperature. Unfortunately after 18 hours analysis revealed no presence of any β-lactam **355** in the ^{1}H NMR spectrum of the crude products. The reaction was repeated numerous times to no avail; therefore it was proposed that the introduction of the methyl substituent must affect the orientaton of the enolate so that it is unable to cyclise effectively onto its imino functionality (Scheme 145).



353 **354** **355**

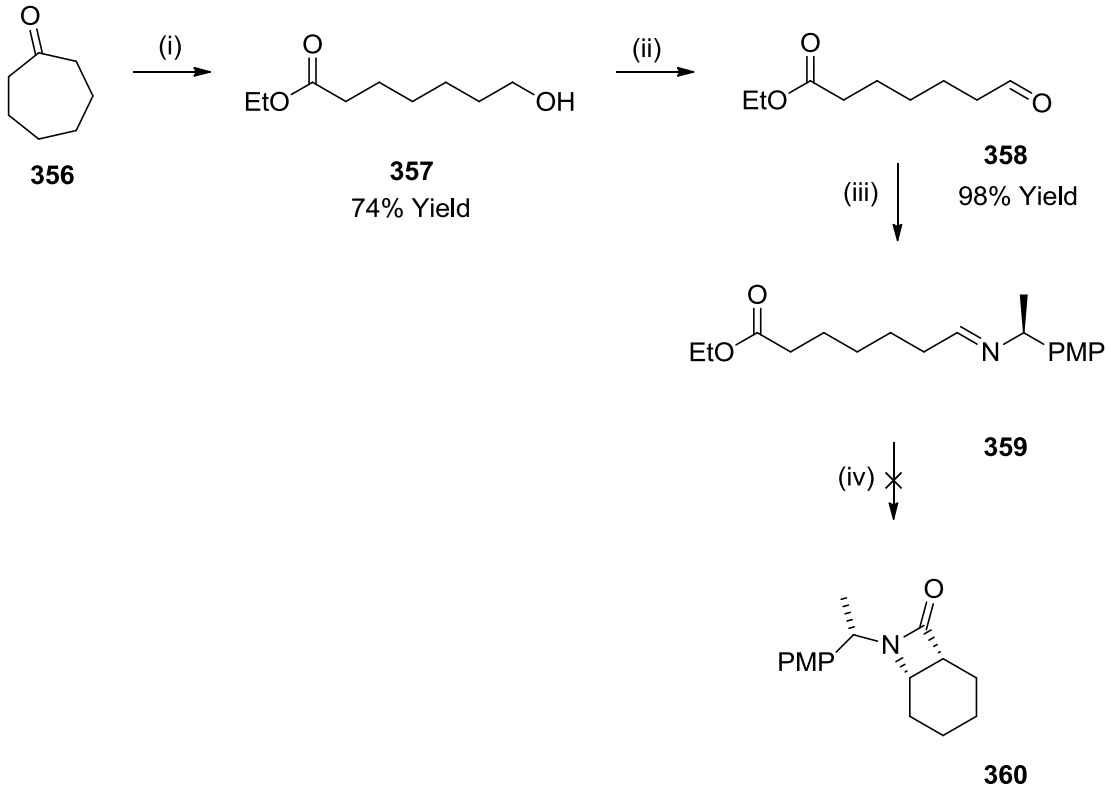
Reagents & Conditions: (i) (S)-α-Methyl-p-methoxybenzylamine, $MgSO_4$, THF 1 hr; (iv) NaHMDS, 15-crown-5, THF, rt, 18 hrs

Scheme 145- Attempted cyclisation of 354 to form (1*R*,2*S*)-2-amino-1-methylcyclopentanecarboxylic acid 355

3.7 Synthesis of Cishexacin

It was decided that the next step in the project was to attempt to increase the size of the aliphatic chain in order to produce cishexacin **360** using our enolate-imine cyclisation reaction. *Trans*-2-aminocyclohexanecarboxylic acid (ACHC) has been widely reported as a monomer for incorporation into β-peptides that display 14 helical conformations.[202] Therefore, an efficient route for the asymmetric synthesis of the analogous cishexacin **360** (Figure 30) would prove invaluable. Once an improved route to cishexacin **360** had been established then the corresponding β-amino ester could be epimerized to give *trans*-ACHC. As can be seen in Scheme 146, the first step was the Baeyer-Villiger oxidation of cycloheptanone **356** with potassium persulphate and subsequent ring opening using ethanol to afford ethyl 7-hydroxyheptanoate **357** in a 74% yield.[203] This was followed by a successful PCC oxidation to furnish the corresponding aldehyde **358** in 98% yield (Scheme 146). During the formation of imine **359**, it was found that after two hours (*S*,*E*)-ethyl 7-((1-(4-methoxyphenyl)ethyl)imino)-heptanoate **359** had started to dimerise due to emergence of a triplet at 5.79 ppm and a singlet at 7.78 ppm in the ^{1}H NMR spectrum. In light of this, it was decided that the imine would be prepared *in situ*, before cyclisation of its enolate was attempted, as previously carried out for cispentacin.

Once the imine **359** had been formed *in situ* the initial cyclisation conditions of NaHMDS and 15-crown-5 at room temperature were applied, however no β-lactam **360** was observed in the ^{1}H NMR spectrum of the crude reaction. Despite several attempts the enolate-imine cyclisation of this substrate was unsuccessful, only affording fragments of recovered starting material fragments. Therefore, it appears that the extra methylene group in the aliphatic chain prevents 6-*endo*-trig cyclisation of the enolate from occurring. In comparison, the synthesis of benzocishexacin **292** was successful, but this might be due to the aryl ring predisposing the derived enolate to cyclise onto its imino functionality.

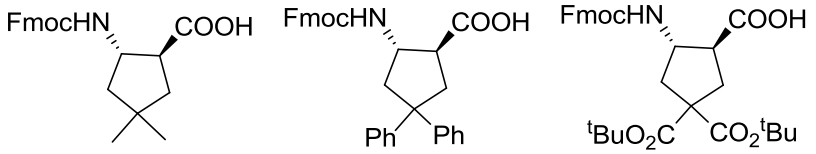


Reagents & Conditions: (i) $K_2S_2O_8$, H_2SO_4, ethanol, rt, 12 hrs; (ii) PCC, DCM; (iii) (S)-α-methyl-p-methoxybenzylamine, $MgSO_4$, DCM, 2 hrs; (iv) NaHMDS (2.0 equiv.), 15-crown-5, THF, rt, 6 hrs

Scheme 146- Attempted synthesis of (1*R*,6*S*)-7-((*S*)-1-(4-methoxyphenyl)ethyl)-7-azabicyclo[4.2.0]octan-8-one 360

3.8 *Gem*-Dimethyl Substituted Cispentacin Synthesis

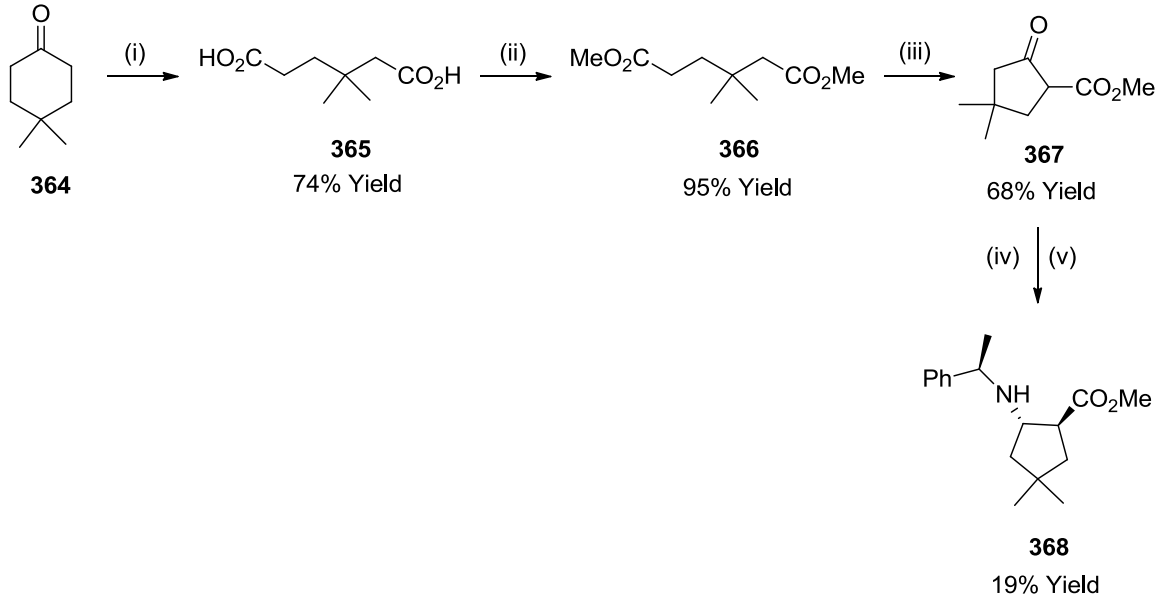
One of the first type of cispentacin analogues prepared was (1*R*,2*S*)-2-amino-4,4-dimethylcyclopentanecarboxylic acid, more commonly referred to as *dm*-ACPC.[204] To date, a review of the literature suggests there are only a few examples of *trans*-4,4-disubstitued ACPC residues having been reported (Figure 34).



361 **362** **363**

Figure 34- Previously synthesised 4,4-disubstituted-ACPC monomers[205]

The *trans-dm*-ACPC residue has recently been incorporated into β-peptides resulting in a 12-helical scaffold,[204] that contains hydrogen bond orientations comparable to those seen in α-peptide helicies.[204] At present there is currently only one reported stereoselective methodology for the synthesis of *dm*-ACPC **368**, which is shown in Scheme 147.

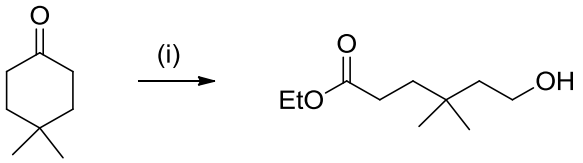


Reagents & Conditions: (i) $KMnO_4$, NaOH, H_2O, rt, 40 hrs; (ii) MeOH, benzene, H_2SO_4; (iii) KO^tBu, THF; (iv) (R)-α-methylbenzylamine, AcOH, MeOH; (v) $NaBH_3CN$

Scheme 147- Asymmetric synthesis of *dm*-ACPC 368[205]

This current method for the synthesis of *dm*-ACPC **368** requires 5 steps, is lengthy (~105 hours) and very low yielding (~9% overall).[205] Therefore, in an effort to improve the existing route, our intramolecular enolate-imine methodology was employed in order to provide an alternative synthesis of *dm*-ACPC.

It was first necessary to synthesise the starting cyclisation substrate from 4,4-dimethylcyclohexanone **364**. A Baeyer Villiger reaction had previously been employed to generate ethyl 7-hydroxyheptanoate **356** from cycloheptanone **357** and was applied to the 4,4-dimethylcyclohexanone **364** generating alcohol **369** (Scheme 148).[203]



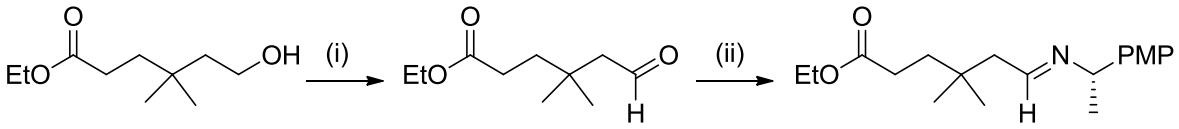
364 **369**

80% Yield

Reagents & Conditions: (i) $K_2S_2O_8$, H_2SO_4, Ethanol, rt, 12 hrs

Scheme 148- Synthesis of ethyl 6-hydroxy-4,4-dimethylhexanoate 369

The corresponding aldehyde **370** was prepared *via* oxidation with PCC in 87% yield, followed by formation of the imine **371** in 87% yield. Imine **371** was left for 72 hours, with ^{1}H NMR analysis revealing it was remarkably stable, with no signs of any new imine products from the enamine-imine dimerisation pathway being formed (Scheme 149).



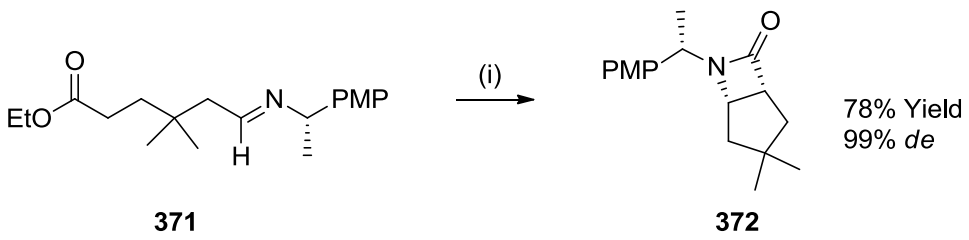
369 **370** **371**

87% Yield 87% Yield

Reagents & Conditions:(i) PCC, DCM; (ii) (S)-α-Methyl-p-methoxybenzylamine, $MgSO_4$, DCM, 2 hrs

Scheme 149- Synthesis of (*S*,*E*)-Ethyl 6-((1-(4-methoxyphenyl)ethyl)imino)-4,4-dimethylhexanoate

Therefore, with the chiral imino ester **371** in hand, the intramolecular enolate-imine cyclisation reaction was attempted in order to generate the protected β–lactam **372**. As with all previous reactions, the cyclisation reaction of **371** was first undertaken at room temperature to maximize the chances of the reaction being successful. It was found that (1*R*,5*S*)-6-((*S*)-1-(4-methoxyphenyl)ethyl)-3,3-dimethyl-6-azabicyclo[3.2.0]heptan-7-one **372** was produced in high 78% yield, but also in 99% *de*. This was dissimilar to the optimum methodology for previous substrates which required the reaction to be cooled to -45 °C and warmed to room temperature to obtain a very high *de* (Scheme 150).



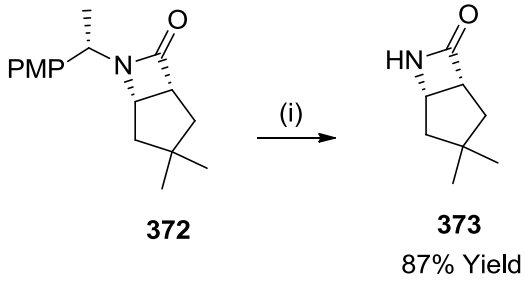
371 **372**

Reagents & Conditions: (i) NaHMDS (2.0 equiv), 15-Crown-5, THF, rt, 6 hrs

Scheme 150- Cyclisation of imine 371 to afford *N*-aryl-β-lactam 372

The yield observed for the *gem*-dimethyl β-lactam **372** was much higher than the yield obtained for cispentacin **336**, which was attributed to the Thorpe-Ingold effect helping cyclisation to occur. In 1915, it was proposed that the introduction of a *gem*-dimethyl group resulted in compression of the internal angle of the nucleophile which favours intramolecular cyclisation reactions.[206] The literature contains many examples where the Thorpe-Ingold effect has had a significant effect on the success of cyclisation reactions. Therefore, it is proposed that the yield of the intramolecular enolate-imine cyclisation is improved due to geminal methyl substituents stabilizing the reactive conformer that leads to enolate cyclisation, and/or due to the fact that the parent imine does not undergo dimerisation.

The removal of the chiral auxiliary fragment from **372** was then carried out using the previously devised CAN methodology (Scheme 151).



372 **373**
87% Yield

Reagents & Conditions: (i) CAN (4.0 equiv.), MeCN-H_2O (1:1), rt, 4 hrs

Scheme 151- Deprotection of β-lactam 372

The β-lactam (1*R*,5*S*)-3,3-dimethyl-6-azabicyclo[3.2.0]heptan-7-one **373** was purified by recrystallisation from dichloromethane and hexane to afford a white solid in 87%

yield, which gave the X-ray crystallographic structure shown in Figure 35, clearly revealing the bicylic β-lactam ring structure.

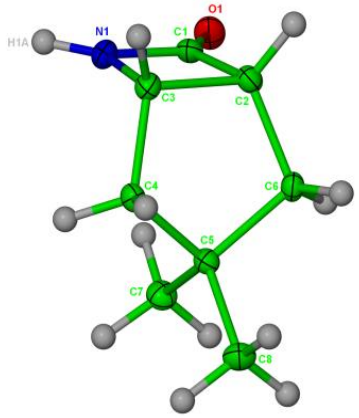
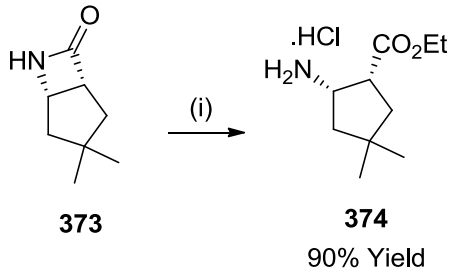


Figure 35- X-ray crystal structure of (1*R*,5*S*)-3,3-dimethyl-6-azabicyclo[3.2.0]heptan-7-one 373 with ellipsoids drawn at the 50% probability level

In addition, the substituted β-lactam **373** could be ring opened using acidic conditions in the presence of ethanol to synthesise (1*R*,2*S*)-ethyl 2-amino-4,4-dimethylcyclopentane carboxylate hydrochloride **374** in 90% yield with a specific rotation value of $[\alpha]_D^{17}$ -2 (*c* 1.01, $CHCl_3$) (Scheme 152).



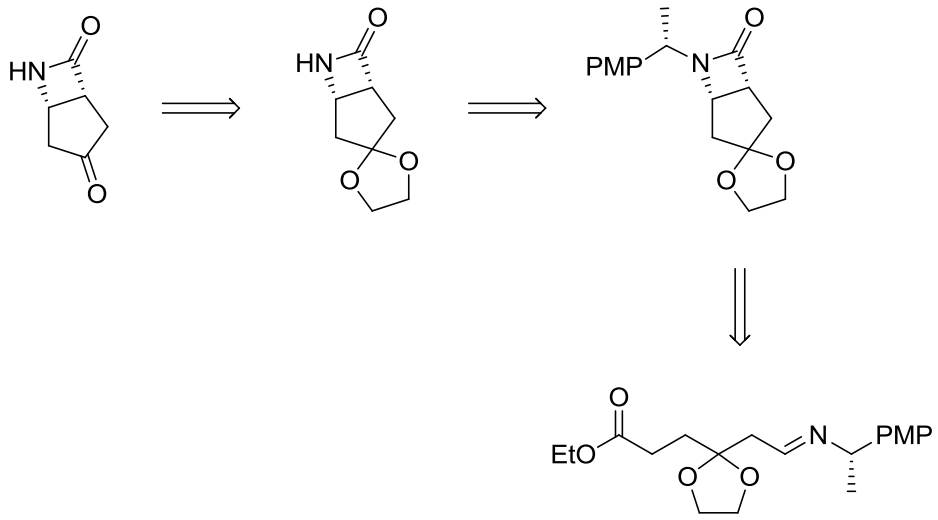
Reagents & Conditions: (i) HCl (1M in Et_2O), EtOH, reflux, 3 hrs

Scheme 152- Synthesis of β-amino ester 374

Therefore, our enolate-imine cyclisation methodology can be used to rapidly prepare β-amino ester **374** in an overall yield of 37% in around 25 hours. Also, unlike previous methodologies chromatographic purification was not required to separate any mixtures of diastereomers.

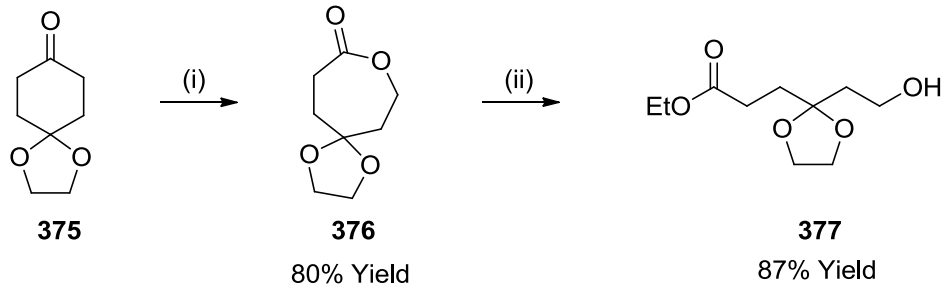
3.9 Cyclisation of Acetal Substituted Cispentacin

In light of the success of the cyclisation reaction to form β-lactam **373** that contains a *gem*-dimethyl substituent it was decided to introduce an acetonide group into the same position. Firstly, it was hoped that the acetonide functionality would function in a similar manner to the *gem*-dimethyl substituent **373**, giving high yields and an excellent *de* for its cyclisation reaction due to the Thorpe-Ingold effect. Also, once enolate cyclisation had taken place, the acetonide group could be removed under mild conditions allowing access to the corresponding ketone (Scheme 153). The ability to generate a β-lactam with a ketone functional group would be highly advantageous as this could potentially allow introduction of a plethora of highly valuable functional groups.



Scheme 153- Retrosynthesis for acetal substituted β-lactam

An alternative set of conditions for the Baeyer-Villiger and ring opening reactions needed to be established that were more basic and compatible with the presence of the acid sensitive acetal protecting group.[207] The use of mCPBA as an oxidant proved successful and the seven-membered lactone **376** was obtained in an 80% yield. The ring opening reaction of the lactone **376** was carried out under basic conditions using K_2CO_3 and ethanol to furnish ethyl 3-(2-(2-hydroxyethyl)-1,3-dioxolan-2-yl)propanoate **377** in an 87% yield (Scheme 154).

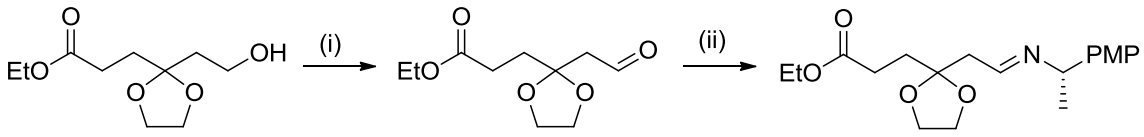


375 **376** 80% Yield **377** 87% Yield

Reagents & Conditions: (i) mCPBA, DCM; (ii) K_2CO_3, EtOH

Scheme 154- Synthesis of ethyl 3-(2-(2-hydroxyethyl)-1,3-dioxolan-2-yl)propanoate 377

From this point, our established methodology was applied involving oxidation of the alcohol **377** using PCC, followed by subsequent imine formation to form **379** in 98% yield. Once again, stability studies revealed that this imine was stable over a period of 48 hours (Scheme 155).



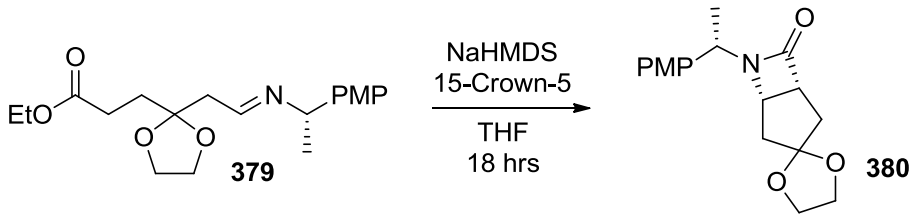
377 **378** 89% Yield **379** 98% Yield

Reagents & Conditions: (i) PCC, DCM; (ii) (S)-α-Methyl-p-methoxybenzylamine, $MgSO_4$, THF, 2 hrs

Scheme 155- Synthesis of (*S,E*)-Ethyl 3-(2-(2-((1-(4-methoxyphenyl)ethyl)imino)ethyl)-1,3-dioxolan-2-yl)propanoate 379

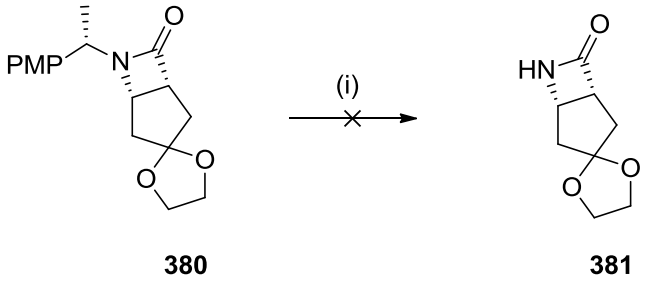
With the imine in hand, the intramolecular enolate-imine cyclisation was attempted both at room temperature, and -45 °C to room temperature, to afford the desired acetal-protected β-lactam **380**. A good 77% yield of the β-lactam **380** was obtained at room temperature in 86% *de*. The optimum conditions of -45 °C to room temperature were then applied and the yield again decreases slightly to 59% but this generated an excellent diastereoselectivity of 98% *de* (Table 17, Entry 2). In comparison with the *gem*-dimethyl cyclisation, it can be seen that the *de* obtained was not as high as observed for the *gem*-dimethyl β-lactam **380** at room temperature. However, when the temperature was reduced to -45 °C the *de* was significantly improved, which was more in line with the results that were observed for cispentacin **336**.

Table 17- Attempted intramolecular enolate-imine cyclisation on imine 379



Entry	Temp (°C)	Yield (%)	*de* (%)
1	rt	77	86
2	-45 °C to rt	59	98

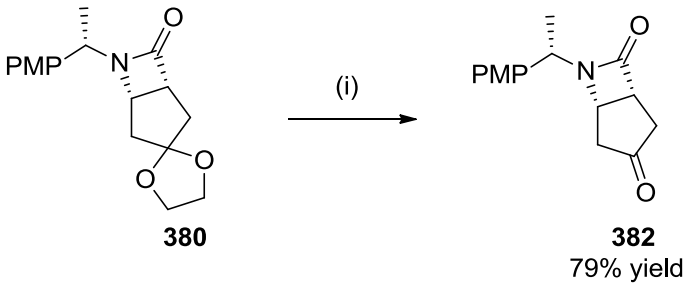
The removal of the chiral auxiliary proved unsuccessful, with only fragments of the starting material being observed in ^{1}H NMR spectra of the crude products.



Reagents & Conditions: (i) CAN (4.0 equiv.), MeCN-H_2O (1:1), rt, 4 hrs

Scheme 156- Removal of chiral auxiliary on β-lactam 380

There is literature precedent for the use of CAN as a mild deprotection reagent for the removal of acetonide groups, which suggested that two competing reactions might be taking place.[208] As such, it was decided to selectively remove the acetal first, to give the ketone functionality, before removal of the chiral auxiliary using an alternative methodology. The use of iodine as a mild deprotection reagent enabled the acetal protecting group to be selectively removed while retaining the β-lactam ring, yielding β-lactam **382** in 79 % yield (Scheme 157).[209]

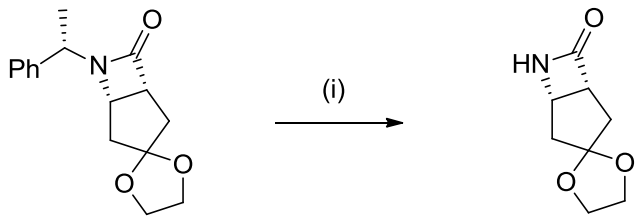


380 **382**
79% yield

Reagents & Conditions: (i) Iodine, acetone, rt, 30 mins

Scheme 157- Synthesis of (1*R*,5*S*)-6-((*S*)-1-(4-methoxyphenyl)ethyl)-6-azabicyclo[3.2.0]heptane-3,7-dione 382

The removal of the auxiliary using CAN was attempted on β-lactam **382**, again this proved unsuccessful with the ^{1}H NMR spectrum of the crude product showing cleaved 1-(4-methoxyphenyl)ethanone but the isolation of any β-lactam was unsuccessful. The problematic removal of the auxiliary suggests that for the synthesis of both β-lactam **381** and β-lactam **382** that an alternative auxiliary would be preferred such as (*S*)-α-methylbenzylamine that could be removed using a hydrogenolytic strategy. Previously, (*S*)-α-methylbenzylamine was avoided due to the symmetry within the tricyclic β-lactam structures, in these bicyclic β-lactams there is no such symmetry (Scheme 158).



383 **384**

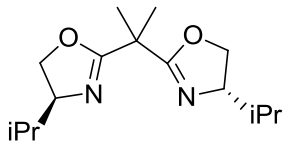
Reagents & Conditions: (i) H_2, Pd/C, rt, 24 hrs

Scheme 158- Proposed deprotection of β-lactam 383 containing an (*S*)-α-methylbenzylamine auxiliary

In conclusion, it has been demonstrated that our enolate-imine cyclisation methodology can also be used to rapidly prepare β-lactams **381** and **382** in high yield and excellent *de*. The removal of the current chiral auxiliary has proved unsuccessful; therefore further work is required in order to successfully generate the free β-lactams of **381** and **382**.

3.10 Future Work - Enantioselective Cyclisation

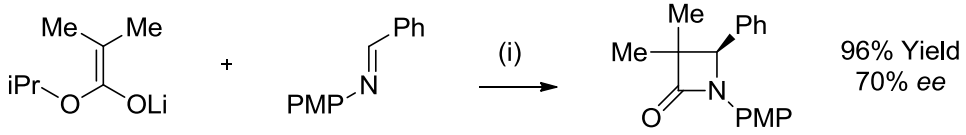
The final work into the intramolecular enolate-imine cyclisation for the synthesis of cispenatcin involved an attempt to control the facial selectivity of the enolate-imine cyclisation reaction in an enantioselective manner. This involved employing an asymmetric Lewis acid catalyst, with the aim of generating *cis* β-lactams in high *ee*. It was decided to employ Tomioka's methodology that had utilised chiral bisoxazoline (BOX) ligands **154** (Figure 36) for the asymmetric synthesis of β-lactams using an *intermolecular* enolate-imine condensation.[81]



154

Figure 36- Isopropyl chiral bisoxazoline ligand

Both high yields and good *ee*'s for β-lactams have been reported using both catalytic and stoichiometric amounts of the copper BOX ligands.[83] In particular, a chiral BOX ligand was shown to mediate an *intermolecular* cyclisation reaction between lithium ester enolates and a benzylic imine, to afford the corresponding β-lactam in 70% *ee* (Scheme 159).

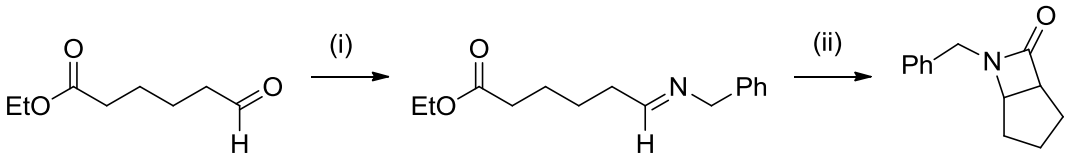


385 **38** **386**

*Reagents & Conditions: (i) i-Pr-BOX ligand **154**(0.2 equiv.), LDA, DCM, -20 ^0C*

Scheme 159- Asymmetric Mannich reaction using (*R*)-iPr-BOX[83]

In order to apply this enantioselective methodology for the asymmetric synthesis of a cispentacin derivative, an achiral imino-ester substrate without a chiral auxiliary group was synthesised. Due to the instability of such imine substrates, the imine **387** was generated *in situ* and an enolate-imine cyclisation reaction carried out, to afford the racemic β-lactam **388** in an unoptimised 30% yield (Scheme 160).



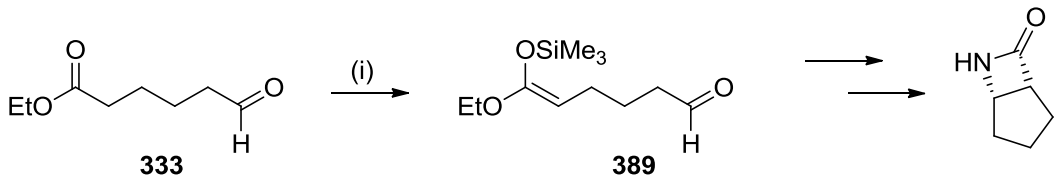
333 **387** **388**

Reagents & Conditions: (i) Benzylamine, mol. sieves, THF, 15 mins; (ii) NaHMDS, rt, 18 hrs.

Scheme 160- Synthesis of racemic cispentacin β-lactam 388

This allowed appropriate chiral HPLC conditions (AS-3, 90% iso-hexane, 10% ethanol) to be developed that gave well resolved peaks for its enantiomers.

Tomioka's conditions were then applied to the cyclisation of imino ester **387** whose enolate was generated in the presence of 0.2 equivalents of the isopropyl-BOX ligand **154**. This reaction was analysed by ^{1}H NMR and showed only the presence of starting material, with no β-lactam having been formed. Therefore, the original cyclisation conditions using NaHMDS in THF at -45 °C to room temperature were applied with the addition of a stoichiometric amount of the chiral BOX ligand **154**, which produced the β-lactam **388**, albeit in a poor 6% yield, which was shown to be racemic by chiral HPLC analysis. The main problems with using this methodology is that when the reaction is carried out in an intermolecular fashion the lithium enolate is first generated, and then the chiral BOX ligand is added, which allows for its complexation to the enolate before the addition of the imine. Unfortunately, for the intramolecular reaction the enolate is always generated in the presence of the imine, so cyclisation can potentially occur before the BOX ligand can have any control over the cyclisation reaction. Enantioselective control of both direct and indirect Mannich reactions has been the subject of several major reviews[210-211] and therefore there are many more approaches that could be taken in this area of work. For example, the enantioselective reaction could be potentially attempted using a silyl ketene acetal as shown in Scheme 161.



333 **389**

Reagents & Conditions: (i) TMS-Cl, LDA, THF, -78 °C

Scheme 161- Potential synthesis of silyl ketene acetal for an indirect Mannich reaction

3.11 Conclusion

In conclusion, our previously developed intramolecular enolate-imine cyclisation reaction has been applied to the asymmetric synthesis of four acyclic β-lactam analogues. An asymmetric synthesis of cispentacin has been developed that also enables the rapid access to the highly desirable transpentacin. An improved methodology for the synthesis of (1*R*,5*S*)-6-((*S*)-1-(4-methoxyphenyl)ethyl)-3,3-dimethyl-6-azabicyclo[3.2.0]heptan-7-one **372** has been developed,g which is not only quicker but also higher yielding than previous syntheses. Furthermore, the limitations of this methodology have been established by unsuccessfully attempting the cyclisations of acyclic enolates of 6-membered and α-methyl substituted ω-imino-esters. Finally, unsuccessful approaches towards an enantioselective intramolecular enolate-imine cyclisation reaction were attempted in order to synthesise a range of β-amino acids enantiomers without the need for a chiral auxiliary.

4 Experimental

General Experimental Details

All reactions were performed under a nitrogen atmosphere in oven-dried apparatus, unless otherwise stated. Anhydrous acetonitrile, dichloromethane and tetrahydrofuran were obtained from an Innovative Technology Inc. PS-400-7 solvent purification system. Petrol refers to the fraction of petroleum ether boiling at 40-60 °C. All other commercially available compounds were used as obtained from the chemical suppliers. Analytical thin layer chromatography was performed using commercially available aluminium backed plates coated with Merck G/UV254 neutral silica. Plates were visualised under UV light (at 254 nm) or by staining with phosphomolybdic acid followed by heating. Flash chromatography was performed using chromatography grade silica, 60 Å particle size 35-70 microns from Fisher Scientific. ^{1}H NMR spectra were recorded at 500 MHz, 400 MHz or 300 MHz and ^{13}C{^{1}H} spectra were recorded at 125 MHz or 75 MHz on a Brüker Avance 500, 400 or 300 spectrometer respectively. Chemical shifts, δ, are quoted in parts per million and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; hep., heptet; m, multiplet; pent., pentet; td, triplet of doublets; app., apparent and br., broad. Coupling constants, *J*, are quoted to the nearest 0.5 Hz. High resolution mass spectra were recorded on a Brüker Daltonics microTOF spectrometer with an electrospray source and external calibration. Masses were recorded in positive electrospray ionisation mode and were introduced by flow injection. Masses are accurate to 5 ppm and data was processed using DataAnalysis software from Brüker Daltonics. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer, using a Universal ATR accessory for sampling, with only selected absorbances quoted as ν in cm^{-1}. Optical rotations were recorded on an Optical Activity Ltd AA-10 automatic polarimeter with a path length of 1 dm; concentrations (c) are quoted in g/100 mL. All capillary melting points were measured using Stuart digital SMP10 melting point apparatus with 1 degree resolution. X-ray data was collected at 150K on a Nonius KappaCCD area detector diffractometer using Mo-Kα radiation (λ = 0.71073 Å). All structures were solved by direct methods and refined on all *F2* data using SHELXL-97 suite of programs, with hydrogen atoms included in idealised positions and refined using the riding model.

4.1 General Procedures

4.1.1 General Procedure 1: Acetal Formation[212]

To a stirred substituted 2-bromobenzadehyde (1.0 equiv.) in toluene (50 mL), 1,3-propanediol (1.5 equiv.) and *p*-toluene sulphonic acid (PTSA) (0.1 equiv.) were added and the resulting solution was heated at reflux under Dean-Stark conditions for 3 hours. After cooling to room temperature, the reaction mixture was washed with water, the organic extract dried using $MgSO_4$ and the solvent evaporated under reduced pressure. The crude compounds were purified by recrystallisation using a suitable solvent system.

4.1.2 General Procedure 2: Heck Reaction of Protected 2-Bromo-benzaldehydes[137]

To a solution of substituted 2-(2-bromophenyl)-1,3-dioxolan (1.0 equiv.) in acetonitrile, palladium(II) acetate (0.05 equiv.) and tri(*o*-tolyl)phosphine (0.10 equiv.) were added. Diisopropylethylamine (3.0 equiv.) and the appropriate acrylate (1.0 equiv.) were added and the mixture was heated at reflux for 24 hours. After cooling to room temperature, the reaction was diluted with water (50 mL) and the aqueous layer extracted with toluene (2 x 50 mL). The combined organic extracts were washed with water (2 x 50 mL) and brine (30 mL) and then dried over $MgSO_4$. The mixture was filtered through a plug of Celite® and then the solvent was removed under reduced pressure. Crude compounds were purified by flash column chromatography.

4.1.3 General Procedure 3: Chemoselective Conjugate Reduction of Esters[138]

Substituted ethyl 3-(2-(1,3-dioxan-2-yl)phenyl)propanoates (2.0 equiv.) were stirred in ethanol (10 mL) for 30 minutes prior to the addition of cobalt(II) chloride hexahydrate (0.02 equiv.). The solution was then cooled to 0 ^{o}C and sodium borohydride (4.0 equiv.) was added. The solution was allowed to warm to room temperature and stirred for up to 48 hours. The reaction was quenched with water (50 mL) and diluted with ethyl acetate (30 mL). The organic layer was separated, washed with brine (50 mL), dried with $MgSO_4$ and the solvent evaporated under reduced pressure. Crude compounds were purified by flash column chromatography.

4.1.4 General Procedure 4: Acetal Deprotection

Substituted ethyl-3-(2-formylphenyl)propanoates were added to a solution of acetic acid: water (7 mL : 3 mL) and left to stir open to the air overnight. The residue was

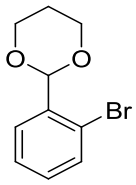
partitioned between water (50 mL) and diethyl ether (50 mL). The aqueous layer was extracted with diethyl ether (2 x 30 mL) and the organic layers were combined and washed with a saturated solution of $NaHCO_3$ (2 x 30 mL) and then brine (30 mL). The organics were dried using $MgSO_4$ and filtered before being evaporated under reduced pressure to yield analytically pure products.

4.1.5 General Procedure 5: Imine-Enolate Cyclisation Reaction

Substituted (*S,E*)-ethyl-3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)propane-ates (1.0 equiv.) were dissolved in THF. 15-Crown-5 (1.1 equiv.) and NaHMDS (1.1 equiv.) were added and the mixture was stirred for 8 hours at -40 ^{o}C. The reaction was quenched with a saturated solution of NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (3 x 30 mL) and the organic layers were combined and washed with water (50 mL). The organics were dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. Crude compounds were purified by flash column chromatography.

4.2 Synthesis of (*S*)-*N*-(α-methyl-p-methoxybenzyl)-ω-imino-esters

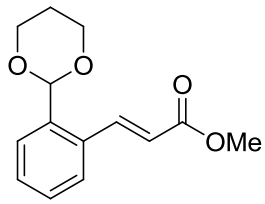
2-(2-Bromophenyl)-1,3-dioxane 210



The title compound was prepared according to General Procedure **1** from 2-bromobenzadehyde **209** (10.0 g, 54 mmol), 1,3-propanediol (6.16 g, 81 mmol) and PTSA (0.86 g, 5.0 mmol). The crude product was purified by recrystallisation from diethyl ether, yielding a white solid (10.47 g, 80 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.59 (1H, dd, J = 8.0 and 1.5 Hz, CBrC*H*), 7.40 (1H, d, J = 8.0 Hz, Ar), 7.20 (1H, t, J = 7.5 Hz, Ar), 7.04 (1H, td, J = 8.0 and 1.5 Hz, Ar), 5.63 (1H, s, ArC*H*), 4.10 (2H, dd, J = 11.0 and 5.0 Hz, OCH_2), 3.85 (2H, td, J = 12.5 and 2.0 Hz, OCH_2), 2.16-1.98 (1H, m, OCH_2CH_2), 1.24 (1H, br. d, J = 13.5 Hz, OCH_2CH_2); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ_C =137.6, 132.6, 130.4, 128.2, 127.6, 122.4, 100.9, 67.6, 25.7; IR (film / cm^{-1}) ν = 2846 (O-CH-O); HRMS: m/z (ES) 243.0018, $C_{10}H_{11}O_2Br$ $[M+H]^+$ requires 243.0021; mp 53-55 ^{o}C.

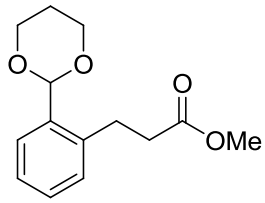
Methyl-3-(2-(1,3-dioxan-2-yl)phenyl)acrylate 211



The title compound was prepared according to General Procedure **2** from 2-(2-bromophenyl)-1,3-dioxolan **210** (2.67 g, 11.0 mmol), methyl acrylate (0.99 mL, 11 mmol), palladium (II) acetate (0.12 g, 0.55 mmol), tri(*o*-tolyl)phosphine (0.33 g, 1.1 mmol) and diisopropylethyl amine (5.7 mL, 33.0 mmol). The crude product was purified using flash column chromatography [Petrol : EtOAc (85:15), R_f 0.28] yielding a yellow oil (2.29 g, 84 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.16 (1H, d, J = 16.0 Hz, ArC*H*CH), 7.57-7.48 (2H, m, Ar), 7.35-7.23 (2H, m, Ar), 6.28 (1H, d, J = 16.0 Hz, ArCHC*H*), 5.63 (1H, s, ArC*H*O), 4.21 (2H, ddd, J = 12.0, 5.0 and 1.5 Hz, OCH_2CH$_2$), 3.94 (2H, td, J = 12.5 and 2.5 Hz, OCH_2CH$_2$), 3.74 (3H, s, OMe), 2.30-2.12 (1H, m, OCH$_2$CH_2), 1.44-1.34 (1H, m, OCH$_2$CH_2); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 167.8, 142.9, 137.6, 133.2, 129.5, 128.5, 127.4, 127.2, 119.9, 100.6, 67.9, 52.1, 26.1; IR (film / cm^{-1}) ν = 1712 (C=O), 1635 (C=C); HRMS: m/z (ES) 249.1116, $C_{14}H_{16}O_4$ $[M+H]^+$ requires 249.1127

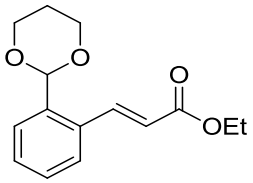
Methyl-3-(2-(1,3-dioxan-2-yl)phenyl)propanoate 212



The title compound was prepared according to General Procedure **3** from methyl 3-(2-(1,3-dioxan-2-yl)phenyl)acrylate **211** (1.46 g, 5.9 mmol) and cobalt(II) chloride hexahydrate (0.01 g, 0.06 mmol) in methanol (30 mL) with the addition of sodium borohydride (0.44 g, 11.8 mmol) and was stirred at room temperature for 48 hours. The crude product was purified using flash column chromatography [Petrol: EtOAc (80:20), R_f 0.79] yielding a brown oil (1.01 g, 70 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.33-7.16 (4H, m, Ar), 5.68 (1H, s, C*H*O$_2$), 4.33-4.24 (2H, m, OCH_2CH$_2$), 4.02 (2H, td, J = 2.5 and 12.0 Hz, OCH_2CH$_2$), 3.71 (3H, s, OCH_3), 3.14- 3.05 (2H, m, ArCH_2CH$_2$), 2.71-2.62 (2H, m, ArCH$_2$CH_2), 2.37-2.17 (1H, m, OCH$_2$CH_2), 1.47 (1H, app d of hep., J = 13.5 and 1.0 Hz, OCH$_2$CH_2).

(*E*)-Ethyl 3-(2-(1,3-dioxan-2-yl)phenyl)acrylate 217

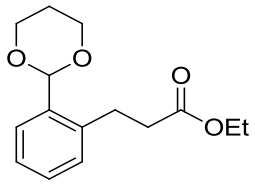


The title compound was prepared according to General Procedure **2** from 2-(2-bromophenyl)-1,3-dioxane **210** (10.8 g, 44.4 mmol), ethyl acrylate (4.82 mL, 44.4 mmol), palladium (II) acetate (0.49 g, 2.2 mmol), tri(*o*-tolyl)phosphine (1.35 g, 4.5

mmol) and diisopropylethyl amine (23.2 mL, 133.4 mmol) in acetonitrile (120 mL). The crude product was purified by flash column chromatography [Petrol : EtOAc (80:20), R_f 0.39] yielding a yellow oil (11.2 g, 96 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.16 (1H, d, J = 16.0 Hz, ArC*H*CH), 7.53 (2H, app. td, J = 2.0 Hz, Ar), 7.35-7.24 (2H, m, Ar), 6.28 (1H, d, J = 16.0 Hz, ArCHC*H*), 5.63 (1H, s, C*H*O), 4.25-4.16 (4H, m, OC*H*$_2$CH$_2$ and OC*H*$_2$CH$_3$), 4.00-3.89 (2H, m, OC*H*$_2$CH$_2$), 2.30-2.13 (1H, diastereotopic m., OCH$_2$C*H*$_2$), 1.40 (1H, app. d of hep., J = 13.5 and 1.5 Hz, OCH$_2$C*H*$_2$), 1.27 (3H, t, J = 7.0 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 167.0, 142.2, 137.1, 132.9, 129.8, 129.1, 127.0, 126.7, 119.9, 100.3, 67.6, 60.5, 25.7, 14.3; IR (film / cm^{-1}) ν = 2851 (O-CH-O), 1728 (C=O), 1608 (C=C); HRMS: m/z (ES) 287.1259, $C_{15}H_{20}O_4$ [M+Na]$^+$ requires 287.1259.

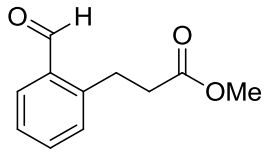
Ethyl 3-(2-(1,3-dioxan-2-yl)phenyl)propanoate 216



The title compound was prepared according to General Procedure **3** from ethyl 3-(2-(1,3-dioxan-2-yl)phenyl)acrylate **217** (1.91 g, 7.7 mmol), cobalt(II) chloride hexahydrate (0.02 g, 0.08 mmol) in ethanol (30 mL) with the addition of sodium borohydride (0.58 g, 15.4 mmol). The crude product was purified using flash column chromatography [Petrol : EtOAc (80:20), R_f 0.74] yielding a yellow oil (1.65 g, 81 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.62-7.57 (1H, m, Ar), 7.31-7.16 (3H, m, Ar), 5.67 (1H, s, ArC*H*O), 4.27 (2H, ddd, J = 10.5, 5.0 and 1.0 Hz, OC*H*$_2$CH$_2$), 4.16 (2H, q, J = 7.0 Hz, OC*H*$_2$CH$_3$), 4.01 (2H, td, J = 2.5 and 12.5 Hz, OC*H*$_2$CH$_2$), 3.12-3.03 (2H, m, ArC*H*$_2$CH$_2$), 2.69-2.59 (2H, m, ArCH$_2$C*H*$_2$), 2.35-2.17 (1H, m, OCH$_2$C*H*$_2$), 1.50-1.41 (1H, m, OCH$_2$C*H*$_2$), 1.27 (3H, t, J = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 173.6, 138.9, 136.8, 129.9, 129.3, 127.0, 126.8, 100.6, 67.7, 60.7, 36.5, 28.3, 26.1, 14.6; IR (film / cm^{-1}) ν = 1729 (C=O); HRMS: m/z (ES) 287.1247, $C_{15}H_{20}NaO_4$ [M+Na]$^+$ requires 287.1259.

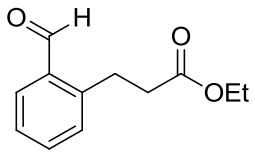
Methyl-3-(2-formylphenyl)propanoate 218



The title compound was prepared according to General Procedure **4** from methyl 3-(2-(1,3-dioxan-2-yl)phenyl)propanoate **212** (1.01 g, 4.1 mmol), which was added to a solution of acetic acid : water (7 mL : 3 mL) and stirred open to the air overnight. The crude product was purified using flash column chromatography [Petrol : EtOAc (75:25), R_f 0.70] yielding a yellow oil (0.57 g, 73 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.14 (1H, s, C*H*O), 7.80-7.77 (1H, m, Ar), 7.48-7.27 (3H, m, Ar), 3.59 (3H, s, OCH_3), 3.29 (2H, t, J = 7.5 Hz, ArCH_2CH$_2$), 2.58 (2H, t, J = 7.5 Hz, ArCH$_2$CH_2); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 193.1, 173.5, 143.2, 134.2, 134.0, 132.3, 127.5, 52.0, 35.7, 28.5; IR (film / cm^{-1}) ν = 1733 (C=O), 1693 (C=O); HRMS: m/z (ES) 193.0854, $C_{11}H_{12}O_3$ [M+H]$^+$ requires 193.0864.

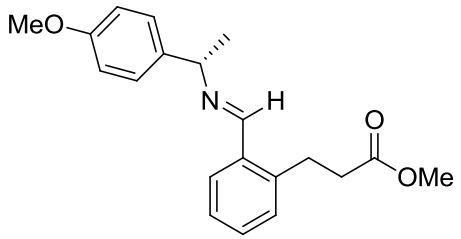
Ethyl 3-(2-formylphenyl)propanoate 219



The title compound was prepared according to General Procedure **4** from ethyl 3-(2-(1,3-dioxan-2-yl)phenyl)propanoate **216** (0.55 g, 2.2 mmol), which was added to a solution of acetic acid : water (7 mL : 3 mL) and stirred open to the air overnight. The crude was purified using flash column chromatography [Petrol : EtOAc (75:25), R_f 0.63] yielding a colourless oil (0.32 g, 75 %).

^{1}H NMR (250 MHz, $CDCl_3$): δ_H = 10.25 (1H, s, ArC*H*O), 7.89-.7.80 (1H, m, Ar), 7.60-7.27 (3H, m, Ar), 4.14 (2H, q, J =7.0 Hz, OCH_2CH$_3$), 3.89 (2H, t, J = 7.5 Hz, ArCH_2CH$_2$), 2.67 (2H, t, J = 7.5 Hz, ArCH_2CH$_2$), 1.25 (3H, t, J = 7.0 Hz, OCH$_2$CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 192.7, 172.6, 142.9, 133.8, 133.8, 133.4, 131.2, 127.0, 60.5, 35.6, 28.0, 14.2; IR (film / cm^{-1}) ν = 1728 (C=O), 1694 (C=O) HRMS: m/z (ES) 207.1009, $C_{12}H_{14}O_3$ [M+H]$^+$ requires 207.1021.

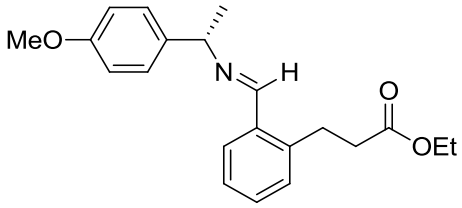
(*S*,*E*)-Methyl-3-(2-(((1-(4-methoxyphenyl)ethyl)imino)methyl)phenyl)propanoate 220



Methyl 3-(2-formylphenyl)propanoate **218** (0.036 g, 0.19 mmol) was dissolved in dry CH_2Cl_2 (3 mL) with $MgSO_4$ and stirred under a nitrogen atmosphere. After 5 minutes, (*S*)-(-)-4-methoxy-α-methylbenzylamine (0.28 mL, 0.19 mmol) was added and the solution was stirred for 5 hours. The solution was filtered and the solvent was evaporated under reduced pressure, yielding a yellow oil (0.058 g, 96 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.60 (1H, s, C*H*N), 7.79 (1H, dd, J = 1.5 and 7.5 Hz, Ar), 7.37-7.18 (5H, m, Ar), 6.91-6.84 (2H, m, Ar), 4.49 (1H, q, J = 7.0 Hz, C*H*CH_3), 3.80 (3H, s, ArOC*H*$_3$), 3.67 (3H, s, COOC*H*$_3$), 3.25 (2H, t, J = 8.0 Hz, C*H*$_2$$CH_2$), 2.61 (2H, t, J = 8.0 Hz, CH_2C*H*$_2$), 1.56 (3H, d, J = 7.0 Hz, CHC*H*$_3$); IR (film / cm^{-1}) ν = 1735 (C=O), 1639 (C=N); HRMS: m/z (ES) 326.1755, $C_{20}H_{23}O_3N$ $[M+H]^+$ requires 326.1756.

(*S*,*E*)-Ethyl-3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)propanoate 221



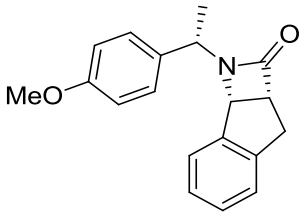
Ethyl 3-(2-formylphenyl)propanoate **219** (4.07 g, 19.8 mmol) was dissolved in dry CH_2Cl_2 (150 mL) with $MgSO_4$ and stirred under a nitrogen atmosphere. After 5 minutes, (*S*)-(-)-4-methoxy-α-methylbenzylamine (2.92 mL, 19.8 mmol) was added and the solution was stirred for 5 hours. The solution was filtered and the solvent was evaporated under reduced pressure yielding a yellow oil (6.34 g, 95 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.67 (1H, s, ArC*H*N), 7.86 (1H, dd, J = 7.5 and 1.5 Hz, Ar), 7.44-7.24 (5H, m, Ar), 6.96-6.92 (2H, m, Ar), 4.55 (1H, q, J = 6.5 Hz, CHC*H*$_3$), 4.19 (2H, q, J = 7.0 Hz, OC*H*$_2$$CH_3$), 3.85 (3H, s, OC*H*$_3$), 3.30 (2H, t, J = 8.0 Hz, ArC*H*$_2$$CH_2$),

2.66 (2H, t, J = 8.0 Hz, $ArCH_2CH_2$), 1.62 (3H, d, J = 6.5 Hz, $CHCH_3$), 1.29 (3H, t, J = 7.0 Hz, CH_2CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C = 173.0, 158.5, 157.9, 140.3, 137.5, 134.1, 130.2, 130.1, 129.5, 127.6, 127.4, 126.7, 114.1, 113.8, 70.1, 60.4, 55.3, 35.9, 28.4, 25.2, 14.2; IR (film / cm^{-1}) ν = 1730 (C=O), 1639 (C=N), 1611 (C-O); HRMS: m/z (ES) 340.1912, $C_{21}H_{25}O_3N$ $[M+H]^+$ requires 340.1913; $[\propto]_D^{25}$= +15.2 (c 1.45, $CHCl_3$).

4.3 Initial Attempts at Developing an Intramolecular Enolate-Imine Cyclisation

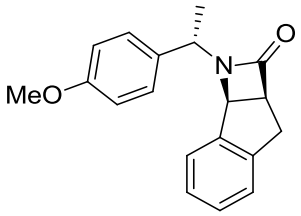
(2a*R*,7b*R*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one 223a



The title compound was prepared according to General Procedure **5** from (*S,E*)-ethyl 3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)propanoate **221** (0.144 g, 0.42 mmol), which was dissolved in THF (10 mL) under a nitrogen atmosphere. 15-Crown-5 (0.09 mL, 0.46 mmol) and NaHMDS (1M in THF, 0.46 mL, 0.46 mmol) was added and the mixture was stirred for 8 hours at -40 °C and allowed to warm to room temperature. The crude product was purified using flash column chromatography [Petrol: EtOAc (60:40), R_f 0.47] yielding a white crystalline solid (0.088 g, 73 %).

^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.34-7.28 (4H, m, Ar), 7.22-7.14 (2H, m, CH_3OCHCH), 6.98-6.94 (2H, m, CH_3OCH), 5.00 (1H, q, J = 7.0 Hz, $CHCH_3$), 4.83 (1H, d, J = 4.5 Hz, CHCHN), 3.92-3.89 (1H, m, $CHCH_2$), 3.88 (3H, s, OCH_3), 3.41 (1H, dd, J = 17.5 and 2.0 Hz, CH_2CH), 3.03 (1H, dd, J = 17.5 and 10.5 Hz, CH_2CH), 1.44 (3H, d, J = 7.0 Hz, $CHCH_3$); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ_C = 169.8, 159.1, 145.1, 139.7, 132.0, 128.8, 128.4, 126.5, 126.4, 126.2, 114.0, 61.4, 55.4, 51.7, 51.2, 30.1, 18.9; IR (film / cm^{-1}) ν = 1731 (C=O) HRMS: m/z (ES) 316.1308, $C_{19}H_{19}O_2N$ $[M+Na]^+$ requires 316.1313; mp 90-92 °C; $[\propto]_D^{25}$ = -52 (*c* 1.15, $CHCl_3$).

(2aS,7bS)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)one 223b

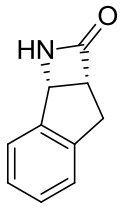


(*S,E*)-Ethyl 3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)propanoate **221** (0.24 g, 0.7 mmol) was dissolved in THF (23 mL). KHMDS (0.5 M in toluene, 1.5 mL, 0.78 mmol) was added and the mixture was stirred for 8 hours at room temperature. The reaction was quenched with a saturated solution of NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL) and the organic layers were combined and washed with NH_4Cl (50 mL) and water (50 mL). The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude product was purified using flash column chromatography [Hexane: Et_2O (1:1), R_f 0.15] yielding a white crystalline solid (0.031 g, 15 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.33-7.28 (2H, m, Ar), 7.24-7.19 (2H, m, Ar), 7.15-7.10 (1H, m, Ar), 6.93-6.86 (3H, m, Ar), 4.82 (1H, d, J = 4.5 Hz, CHC*H*N), 4.48 (1H, q, J = 7.0 Hz, C*H*CH_3), 3.92-3.89 (1H, m, C*H*CH_2), 3.86 (3H, s, OC*H*$_3$), 3.40 (1H, dd, J = 17.5 and 2.0 Hz, C*H*$_2$CH), 3.07 (1H, dd, J = 17.5 and 10.5 Hz, C*H*$_2$CH), 1.71 (3H, d, J = 7.0 Hz, CHC*H*$_3$); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C = 170.3, 159.0, 144.9, 138.9, 133.4, 128.8, 128.1, 126.5, 126.4, 125.8, 114.1, 61.1, 55.4, 53.9, 51.5, 30.3, 20.8; IR (film / cm^{-1}) ν = 1737 (C=O); HRMS: m/z (ES) 294.1502, $C_{19}H_{19}O_2N$ $[M+H]^+$ requires 294.1494; mp 93-95 °C; $[\propto]_D^{17}$ = +37.3 (*c* 0.375, $CHCl_3$).

4.4 Determination of the Configuration of β-Lactam 223

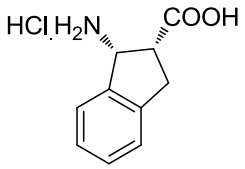
(2a*R*,7b*R*)-2a,3-Dihydro-1H-indeno[1,2-b]azet-2(7bH)-one 198a



(2a*R*,7b*R*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one (0.035 g, 0.12 mmol) **223a** was added to a solution of acetonitrile : water (7.5 mL : 1.5 mL). Ammonium cerium(IV) nitrate (0.19 g, 0.35 mmol) was added portion-wise and the solution was left to stir for 16 hours. The reaction was then quenched with a saturated solution of $NaHCO_3$ (30 mL) and diluted with diethyl ether (30 mL). The aqueous layer was extracted with diethyl ether (2 x 30 mL) and the organic layers combined and washed with a saturated solution of $NaHCO_3$ (2 x 30 mL) The organics were dried using $MgSO_4$ and filtered, before being evaporated under reduced pressure. The crude product was purified by recrystallisation from dichloromethane and hexane yielding a white crystalline solid (0.14 g, 76 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.35-7.21 (4H, m, Ar), 6.25 (1H, br. s, N*H*), 5.03 (1H, d, J = 4.5 Hz, NC*H*CH), 4.06-4.00 (1H, m, C*H*CH_2), 3.35 (1H, d, J = 17.5 Hz, CHC*H*$_2$), 3.07 (1H, dd, J = 17.5 and 10.5 Hz, CHC*H*$_2$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 170.5, 143.2, 139.5, 128.1, 126.1, 125.3, 124.1, 57.5, 53.2, 29.3; IR (film / cm^{-1}) ν = 3164 (N-H), 1695 (C=O); HRMS: m/z (ES) 182.0581, $C_{10}H_9ON[M+Na]^+$ requires 181.0582; mp 191-192 °C; $[\propto]_D^{21}$ = -214 (*c* 0.69, $CHCl_3$).

(1*R*,2*R*)-1-Amino-2,3-dihydro-1H-indene-2-carboxylic acid hydrochloride 189a

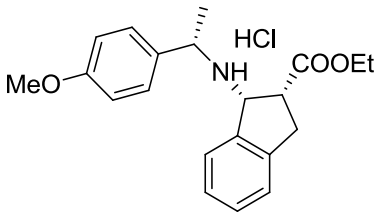


(2a*R*,7b*R*)-2a,3-Dihydro-1H-indeno[1,2-b]azet-2(7bH)-one **198a** (0.020 g, 0.13 mmol) was added to 18% HCl (5mL) and the solution was heated at reflux for 3 hours. The solvent was then evaporated under reduced pressure. The crude product was purified by recrystallisation from ethanol and diethyl ether yielding a white crystalline solid (0.022 g, 83 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.45 (1H, d, J = 8.0 Hz, Ar), 7.40-7.34 (2H, m, Ar), 7.31 (1H, t, J = 7.0 Hz, Ar), 4.94 (1H, d, J = 6.5 Hz, NC*H*), 3.69 (1H, q, J = 8.0 Hz, NCHC*H*), 3.30 (2H, d, J = 8.5 Hz, CHCH_2); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ_C = 175.4, 142.1, 136.6, 130.3, 127.7, 125.4, 125.3, 55.3, 45.5, 33.3; IR (film / cm^{-1}) ν = 3384 (O-H), 1715 (C=O); HRMS: m/z (ES) 200.0680, $C_{10}H_{11}O_2N$ $[M+Na]^+$ requires 200.0687; mp 210-214 °C; $[\propto]_D^{25}$ = -2.5 (*c* 0.4, MeOH).

4.5 Occurrence of a Minor β-Amino Ester Side Product

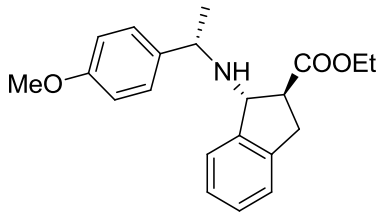
(1*R*,2*R*)-Ethyl-1-((*S*)-1-(4-methoxyphenyl)ethylamino)-2,3-dihydro-1H-indene-2-carboxylate hydrochloride 242



(2a*R*,7b*R*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one **223b** (0.12 g, 0.40 mmol) was heated at reflux in ethanol (21 mL) with dry HCl (1 M in Et_2O, 9 mL) for 2 hours. The solvent was then evaporated under reduced pressure. The crude product was purified by recrystallisation from ethanol and diethyl ether yielding a white crystalline solid (0.13 g, 94 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 10.56 (1H, s, N*H*), 9.81 (1H, s, N*H*), 8.13 (1H, app. t, Ar), 7.36-7.32 (2H, m, Ar), 7.32-7.28 (2H, m, Ar), 7.16 (1H, app. t, Ar), 6.88 (2H, d, J = 8.5 Hz, Ar), 4.99 (1H, t, J = 6.5 Hz, NHC*H*CH), 4.24 (2H, q, J = 7.0 Hz, OC*H*$_2$CH$_3$), 4.13 (1H, br. s, C*H*CH$_3$), 3.82 (3H, s, OC*H*$_3$), 3.45 (1H, q, J = 8.0 Hz, CH$_2$C*H*), 3.10 (1H, dd, J= 16.0 and 8.5 Hz, C*H*$_2$CH), 2.74 (1H, dd, J = 16.0 and 7.0 Hz, C*H*$_2$CH), 1.79 (3H, d, J = 7.0 Hz, C*H*CH$_3$), 1.31 (3H, t, J = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ_C = 173.2, 160.4, 141.6, 134.9, 130.1, 129.9, 128.2, 127.9, 127.5, 124.6, 114.4, 62.3, 60.3, 57.8, 55.4, 44.6, 34.5, 21.3, 14.0; IR (film / cm^{-1}) ν = 1723 (C=O), 3651 (N-H); HRMS: m/z (ES) 340.1885, $C_{21}H_{25}NO_3$ $[M+H]^+$ requires 340.1913.

(1*R*,2*S*)-Ethyl-1-((*S*)-1-(4-methoxyphenyl)ethylamino)-2,3-dihydro-1H-indene-2-carboxylate 241[124]

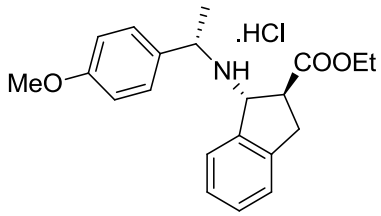


(1*R*,2*R*)-Ethyl-1-((S)-1-(4-methoxyphenyl)ethylamino)-2,3-dihydro-1H-indene-2-carboxylate hydrochloride **242** (0.13 g, 0.37 mmol) was dissolved in dry ethanol (10 mL) under a nitrogen atmosphere. Sodium ethoxide (0.07 g, 0.97 mmol) was added and the reaction was heated at reflux for 7 hours. After cooling, the reaction was quenched with ammonium chloride (5 mL) and the aqueous layer extracted with dichloromethane (2 x 30 mL). The combined organics were collected and washed with water (2 x 30 mL) and then dried over $MgSO_4$. The solvent was then evaporated under reduced pressure.The crude product was purified using flash column chromatography [Petrol : EtOAc (90:10), R_f 0.56] yielding a yellow oil (0.08 g, 62 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.36 (2H, d, J = 8.5 Hz, Ar), 7.27-7.17 (4H, m, Ar), 6.91 (2H, d, J = 8.5 Hz, Ar), 4.38 (1H, d, J = 7.5 Hz, NHC*H*CH), 4.24 (2H, q, J = 7.0 Hz, OC*H*$_2$CH$_3$), 3.96 (1H, q, J = 6.5 Hz, C*H*CH$_3$), 3.83 (3H, s, OC*H*$_3$), 3.48 (1H, q, J = 7.5 Hz, C*H*CH$_2$), 3.32 (1H, dd, J = 16.0 and 5.0 Hz, CHC*H*$_2$), 2.98 (1H, dd, J = 16.0 and 8.0 Hz), 1.38-1.33 (6H, m, OCH$_2$C*H*$_3$ and CHC*H*$_3$); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ_C = 173.8, 158.7, 144.1, 141.0, 137.9, 127.9, 127.8, 126.7, 124.5, 124.2, 113.8, 62.6, 60.5,

55.7, 55.3, 48.7, 33.8, 24.8, 14.4; IR (film / cm^{-1}) ν = 1723 (C=O); HRMS: m/z (ES) 362.1797, $C_{21}H_{25}NO_3$ $[M+Na]^+$ requires 362.1732; $[\propto]_D^{25}$ = -28 (*c* 0.94, $CHCl_3$).

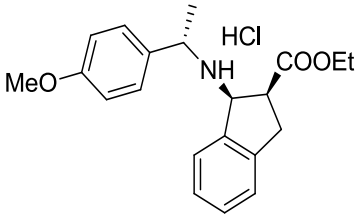
(1*R*,2*S*)-Ethyl-1-((*S*)-1-(4-methoxyphenyl)ethylamino)-2,3-dihydro-1H-indene-2-carboxylate hydrochloride 243



(1*R*,2*S*)-Ethyl-1-((*S*)-1-(4-methoxyphenyl)ethylamino)-2,3-dihydro-1H-indene-2-carboxylate **241** (0.051 g, 0.15 mmol) was dissolved in HCl (1 M solution in Et_2O, 0.15 mL, 0.15 mmol) in Et_2O (4 mL) for 30 minutes. The solvent was then evaporated under reduced pressure affording a white solid (0.056 g, 99 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 10.43 (1H, br. s, HCl), 9.74 (1H, br. s, HCl), 7.88 (1H, d, J = 7.0 Hz, Ar), 7.36 (2H, d, J = 8.0 Hz, C*H*CHOCH$_3$), 7.25 (2H, m, Ar), 7.10 (1H, d, J = 6.5 Hz, Ar), 6.85 (2H, d, J = 8.0 Hz, C*H*OCH$_3$), 4.80 (1H, app. br. s, NHC*H*CH), 4.26-4.17 (3H, m, OC*H*$_2$CH$_3$ and C*H*CH$_3$), 3.77 (3H, s, OC*H*$_3$), 3.38 (1H, q, J = 8.0 Hz, C*H*CH$_2$), 3.32 (1H, dd, J = 16.0 and 8.5 Hz, CHC*H*$_2$), 2.92 (1H, dd, J = 16.0 and 8.0 Hz), 1.68 (3H, d, J = 7.0 Hz, CHC*H*$_3$), 1.27 (3H, t, J = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ_C = 173.0, 160.3, 141.6, 135.0, 130.0, 129.9, 128.3, 127.8, 127.5, 124.6, 114.4, 62.2, 60.3, 55.4, 55.4, 44.9, 34.5, 21.2, 14.0; IR (film / cm^{-1}) ν = 1722 (C=O); HRMS: m/z (ES) 362.1759, $C_{21}H_{25}NO_3$ $[M+Na]^+$ requires 362.1732.

(1*S*,2*S*)-Ethyl-1-(((*S*)-1-(4-methoxyphenyl)ethyl)amino)-2,3-dihydro-1H-indene-2-carboxylate hydrochloride 244

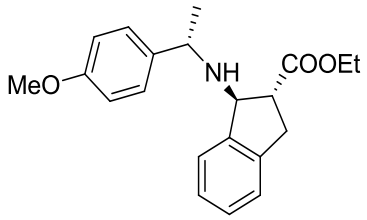


(2aS,7bS)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one **223b** (0.011 g, 0.037 mmol) was heated at reflux in ethanol (2.1 mL) with dry HCl

(1M in Et_2O, 0.9 mL) for 5 hours. The solvent was then evaporated under reduced pressure yielding a yellow oil (0.0136 g, 96 %).

^{1}H NMR (500 MHz, MeOD): δ_H = 7.60 (1H, d, J = 7.5 Hz, Ar), 7.54 (2H, d, J = 8.5 Hz, Ar), 7.46-7.35 (3H, m, Ar), 7.07 (2H, d, J = 8.5 Hz, Ar), 4.75 (1H, d, J = 6.5 Hz, NHC*H*CH), 4.66 (1H, q, J = 6.5 Hz C*H*CH_3), 4.33-4.24 (2H, m, OC*H*$_2$$CH_3$), 3.84 (3H, s, OC*H*$_3$), 3.69-3.62 (1H, m, CH_2C*H*), 3.42-3.32 (2H, m, C*H*$_2$CH), 1.72 (3H, d, J = 6.5 Hz, C*H*CH_3), 1.32 (3H, t, J = 7.0Hz, OCH_2C*H*$_3$); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ_C = 173.9, 160.3, 143.6, 134.3, 130.7, 128.7, 128.4, 127.5, 126.2, 125.9, 115.3, 62.7, 59.3, 56.6, 55.6, 45.6, 34.5, 22.4, 14.1; IR (film / cm^{-1}) ν = 1727 (C=O); HRMS: m/z (ES) 340.1968, $C_{21}H_{25}NO_3$ $[M+H]^+$ requires 340.1913.

(1*S*,2*R*)-Ethyl-1-((*S*)-1-(4-methoxyphenyl)ethylamino)-2,3-dihydro-1H-indene-2-carboxylate 240



(*S,E*)-Ethyl 3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)propanoate **221** (0.060 g, 0.18 mmol) was dissolved in THF (6 mL). KHMDS (0.5 M in toluene, 0.39 mL, 0.19 mmol) was added and the mixture was stirred for 8 hours at room temperature. The reaction was quenched with a saturated solution of NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (3 x 30 mL) and the organic layers were combined and washed with NH_4Cl (50 mL) and water (50 mL), dried over $MgSO_4$ and then evaporated under reduced pressure. The crude product was purified using flash column chromatography [Petrol: EtOAc (70:30), R_f 0.74] yielding a yellow oil (0.011 g, 18 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.40 (3H, d, J = 7.5 Hz, Ar), 7.25-7.19 (2H, m, Ar), 7.19-7.16 (1H, m, Ar), 6.91 (2H, d, J = 8.5 Hz), 4.45 (1H, br. d, J = 3.5 Hz, NHC*H*CH), 4.19-4.06 (3H, m, C*H*CH_3 and OC*H*$_2$$CH_3$), 3.82 (3H, s, OC*H*$_3$), 3.36-3.25 (1H, br. s, C*H*$_2$CH), 3.18-3.06 (2H, m, C*H*$_2$C*H*), 1.35 (3H, d, J = 6.5 Hz, C*H*CH_3), 1.24 (3H, t, J = 7.0 Hz, OCH_2C*H*$_3$); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ_C = 175.3, 158.7, 143.8, 140.7, 137.2, 130.6, 127.9, 126.9, 124.6, 124.3, 113.8, 64.8, 60.7, 55.3, 53.3, 35.0, 26.4, 25.5,

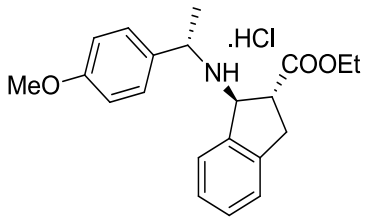
14.2; IR (film / cm^{-1}) ν = 1726 (C=O); HRMS: m/z (ES) 340.1899, $C_{21}H_{25}O_3N$ $[M+H]^+$ requires 340.1913; $[\propto]_D^{25}$ = +21 (*c* 0.99, $CHCl_3$).

The stereochemistry was confirmed using the following experimental method:

(1*S*,2*S*)-Ethyl-1-(((*S*)-1-(4-methoxyphenyl)ethyl)amino)-2,3-dihydro-1H-indene-2-carboxylate hydrochloride **244** (0.015 g, 0.039 mmol) was dissolved in dry ethanol (3 mL) under a nitrogen atmosphere. Sodium ethoxide (0.007 g, 0.10 mmol) was added and the reaction was heated at reflux for 48 hours. After cooling, the reaction was quenched with a saturated solution of NH_4Cl (5 mL) and the aqueous layer extracted with dichloromethane (2 x 20 mL). The combined organics were collected and washed with water (2 x 20 mL) and then dried over $MgSO_4$. The solvent was then evaporated under reduced pressure.[124] The crude was purified using flash column chromatography [Petrol: EtOAc (70:30), R_f 0.74] yielding a yellow oil (0.011 g, 81 %).

Data for this compound identical to that reported above.

(1*S*,2*R*)-Ethyl-1-((*S*)-1-(4-methoxyphenyl)ethylamino)-2,3-dihydro-1H-indene-2-carboxylate hydrochloride 245



(1*S*,2*R*)-Ethyl-1-((*S*)-1-(4-methoxyphenyl)ethylamino)-2,3-dihydro-1H-indene-2-carboxylate **240** (0.062 g, 0.18 mmol) was dissolved in HCl (1M solution in Et_2O, 0.18 mL, 0.18 mmol) and diluted in Et_2O (4 mL) for 30 minutes. The solvent was then evaporated under reduced pressure affording a white solid (0.067 g, 98 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 10.24 (1H, br. s, HCl), 9.74 (1H, br. s, HCl), 7.67 (3H, d, J = 7.0 Hz, Ar), 7.22-7.12 (3H, m, Ar), 6.96 (2H, d, J = 7.5 Hz), 4.68 (1H, d, J = 7.0 Hz, NHC*H*CH), 4.21-4.08 (3H, m, C*H*CH_3 and OC*H*$_2$$CH_3$), 3.83 (3H, s, OC*H*$_3$), 3.80-3.72 (1H, m, C*H*$_2$CH), 3.16 (2H, m, C*H*$_2$C*H*), 1.28 (3H, d, J = 6.0 Hz, C*H*CH_3), 1.22 (3H, t, J = 7.0 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ_C = 172.8, 160.2, 143.1, 134.9, 129.8, 128.4, 127.5, 127.1, 124.5, 124.3, 114.6, 63.3, 61.5, 58.1, 55.3, 46.1,

35.4, 20.3, 14.2; IR (film / cm^{-1}) ν = 1732 (C=O); HRMS: m/z (ES) 340.1897, $C_{21}H_{25}O_3N$ $[M+H]^+$ requires 340.1913.

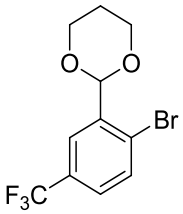
4.6 Development of Benzocispentacin Analogues

2-(2-Bromo-4-methylphenyl)-1,3-dioxane 275a

The title compound was prepared according to General Procedure **1** from 2-bromo-4-methylbenzaldehyde **274a** (0.56 g, 2.8 mmol), 1,3-propanediol (0.30 mL, 4.2 mmol) and PTSA (0.05 g, 0.2 mmol). The crude product was purified by recrystallisation from diethyl ether, yielding a pale yellow oil (0.61 g, 85%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.47 (1H, d, J = 8.0 Hz, CBrC*H*), 7.26 (1H, d, J = 1.0 Hz, Ar), 7.04 (1H, d, J = 8.0 Hz, Ar), 5.63 (1H, s, ArC*H*), 4.18-4.10 (2H, app. ddd, J = 12.0, 5.0 and 1.0 Hz, OCH_2), 3.95-3.85 (2H, m, OCH_2), 2.21 (3H, s, ArCH_3), 2.18-2.04 (1H, m, OCH_2CH_2), 1.32 (1H, app. d of hep., J = 13.5 and 1.5 Hz, OCH_2CH_2); ^{13}C{^{1}H NMR (75 MHz, $CDCl_3$): δ_C = 140.6, 134.7, 133.0, 128.3, 127.8, 122.1, 101.0, 67.6, 25.7, 20.9; IR (film / cm^{-1}) ν = 2851 (O-CH-O); HRMS: m/z (ES) 279.0002, $C_{11}H_{13}O_2Br$ $[M+Na]^+$ requires 278.9997.

2-(2-Bromo-5-(trifluoromethyl)phenyl)-1,3-dioxane 275b

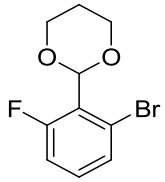


The title compound was prepared according to General Procedure **1** from 2-bromo-5-(trifluoromethyl)benzaldehyde **274b** (3.59 g, 14.2 mmol), 1,3-propanediol (1.5 mL, 21.3 mmol) and PTSA (0.24 g, 1.4 mmol). The crude product was purified by column

chromatography [Petrol : EtOAc (80:20), R_f 0.88] to afford the title compound as a pale yellow oil (3.50 g, 79 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.89 (1H, d, J = 2.5 Hz, Ar), 7.56 (1H, d, J = 8.0 Hz, Ar), 7.37-7.32 (1H, dd, J = 8.5 and 2.5 Hz, Ar), 5.66 (1H, s, ArC*H*), 4.23-4.14 (2H, ddd, J = 12.0, 5.0 and 1.0 Hz, OCH_2), 3.98-3.88 (2H, m, OCH_2), 2.25-2.06 (1H, m, OCH_2CH_2), 1.37 (1H, m, OCH_2CH_2); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C = 138.6, 133.2, 130.1 (q, J = 33 Hz, *C*CF_3), 126.9-126.8 (q, J = 3.5 Hz, *C*HCCF_3), 126.18 (d, J = 1.5 Hz, *C*HCCF_3), 125.6-125.3 (q, J = 3.80 Hz, *C*Br), 125.6-122.0 (q, J = 272.0 Hz, *C*F_3), 100.0, 67.6, 25.6; IR (film / cm^{-1}) ν = 2855 (O-CH-O).

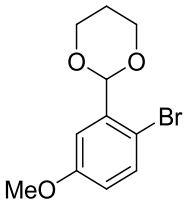
2-(2-Bromo-6-fluorophenyl)-1,3-dioxane 275c



The title compound was prepared according to General Procedure **1** from 2-(2-bromo-6-fluorophenyl)-1,3-dioxane **274c** (0.93 g, 4.6 mmol), 1,3-propanediol (0.49 mL, 6.8 mmol) and PTSA (0.09 g, 0.5 mmol). The crude product was purified by recrystallisation from diethyl ether, to afford the title compound as a white solid (0.60 g, 50 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.29 (1H, d, J = 8.0 Hz, CFC*H*), 7.13-7.04 (1H, app. td, J = 8.0 and 5.5 Hz, CBrC*H*), 7.02-6.93 (1H, m, CHC*H*), 5.96 (1H, s, ArC*H*), 4.25-4.18 (2H, app. dd, J = 12.0 and 5.0 Hz, OCH_2), 3.96-3.86 (2H, t, J = 12.5 Hz, OCH_2), 2.35-2.18 (1H, m, OCH_2CH_2), 1.37 (1H, d of app. hep., J = 13.5 and 1.0 Hz, OCH_2CH_2); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C = 159.8, 131.1 (d, J = 9.5 Hz, CH*C*H), 129.0 (d, J = 3.8 Hz, CBr*C*H), 123.0, 116.2, 115.9, 100.7, 67.8, 25.6; IR (film / cm^{-1}) ν = 2851 (O-CH-O); HRMS: m/z (ES) 282.9738, $C_{10}H_{10}O_2BrF$ $[M+Na]^+$ requires 282.9746; mp 59-60 °C.

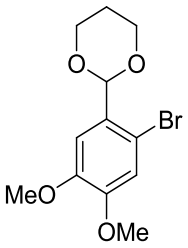
2-(2-Bromo-5-methoxyphenyl)-1,3-dioxane 275d



The title compound was prepared according to General Procedure **1** from 2-bromo-5-methoxybenzaldehyde **274d** (0.47 g, 2.2 mmol), propan-1,3,diol (0.24 mL, 3.3 mmol) and PTSA (0.04 g, 0.2 mmol). The crude product was purified by recrystallisation from diethyl ether, yielding a white solid (0.58 g, 96 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.32 (1H, br. d, J = 9.0 Hz, Ar), 7.17 (1H, d, J = 3.0 Hz, Ar), 6.69 (1H, dd, J = 8.5 and 3.0 Hz, Ar), 5.64 (1H, s, C*H*O), 4.19 (2H, ddd, J = 12.0, 5.0 and 1.0 Hz, OC*H*$_2$CH$_2$), 3.95 (2H, app. br. t, OC*H*$_2$CH$_2$), 3.73 (3H, s, OC*H*$_3$), 2.30-2.08 (1H, m, OCH$_2$C*H*$_2$), 1.37 (1H, app. d of hep., J = 13.5 and 1.5 Hz, OC*H*$_2$CH$_2$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 159.5, 138.7, 133.6, 117.5, 113.1, 113.0, 101.2, 68.0, 55.9, 26.1; IR (film / cm^{-1}) ν = 2853 (O-CH-O); HRMS: m/z (ES) 273.0129, $C_{11}H_{13}O_3Br$ $[M+H]^+$ requires 273.0126, mp 79-81 °C.

2-(6-Bromo-2,3-dimethoxyphenyl)-1,3-dioxane 275e

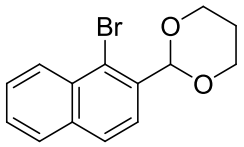


The title compound was prepared according to General Procedure **1** from 6-bromoveratraldehyde **274e** (2.03 g, 8.3 mmol), 1,3-propanediol (0.9 mL, 12.4 mmol) and PTSA (0.14 g, 0.8 mmol). The crude was purified by recrystallisation from diethyl ether, yielding a white solid (2.11 g, 84 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.21 (1H, s, Ar), 6.99 (1H, s Ar), 5.70 (1H, s, C*H*O), 4.27 (2H, ddd, J = 12.0, 6.5 and 1.5 Hz, OC*H*$_2$CH$_2$), 4.08-3.97 (2H, m, OC*H*$_2$CH$_2$), 3.91 (3H, s, OMe), 3.87 (3H, s, OC*H*$_3$), 2.35-2.16 (1H, m, OCH$_2$C*H*$_2$), 1.46 (1H, app. d of

hep., J = 13.5 and 1.5 Hz, OCH_2CH_2); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C = 150.2, 149.0, 130.2, 115.5, 112.9, 110.7, 101.4, 68.0, 56.6, 56.4, 26.0; IR (film / cm^{-1}) ν = 2855 (O-CH-O); HRMS: m/z (ES) 303.0232, $C_{12}H_{15}O_4Br$ $[M+H]^+$ requires 303.0232; mp 98-99 °C.

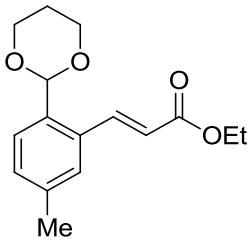
2-(1-Bromonaphthalen-2-yl)-1,3-dioxane 275f



The title compound was prepared according to General Procedure **1** from 2-(1-bromonaphthalen-2-yl)-1,3-dioxane **274f** (1.46 g, 6.2 mmol), propan-1,3-diol (0.67 mL, 9.3 mmol) and PTSA (0.10 g, 0.6 mmol). The crude was purified by recrystallisation from diethyl ether, yielding a white solid (1.53 g, 84 %).

^1H NMR (300 MHz, $CDCl_3$): 8.38 (1H, app. d, J = 8.5 Hz, Ar), 7.88 (3H, m, Ar), 7.50 (2H, m, Ar), 6.11 (1H, s, ArC*H*), 4.36-4.28 (2H, ddd, J = 12.0, 5.0 and 1.5 Hz, OCH_2), 4.16-4.05 (2H, m, OCH_2), 2.40-2.22 (1H, m, OCH_2CH_2), 1.49 (1H, app d of hep., J = 13.5 and 1.5 Hz, OCH_2CH_2); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C = 135.6, 134.8, 132.0, 128.2, 128.0, 127.4, 127.3, 127.0, 124.6, 123.0, 102.0, 67.7, 25.8; IR (film / cm^{-1}) ν = 2864 (O-CH-O); HRMS: m/z (ES) 293.0164, $C_{14}H_{13}O_2Br$ $[M+H]^+$ requires 293.0177.

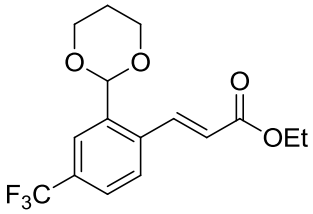
(*E*)-Ethyl 3-(2-(1,3-dioxan-2-yl)-5-methylphenyl)acrylate 276a



The title compound was prepared according to General Procedure **2** from 2-(2-bromo-4-methylphenyl)-1,3-dioxane **275a** (0.96 g, 3.7 mmol), ethyl acrylate (0.40 mL, 3.7 mmol), palladium (II) acetate (0.04 g, 0.19 mmol), tri(*o*-tolyl)phosphine (0.11 g, 0.37 mmol) and diisopropylethyl amine (1.95 mL, 11.2 mmol) in acetonitrile (30 mL). The crude product was purified by column chromatography [Petrol : EtOAc (90:10), R_f 0.20] yielding a yellow oil (0.74 g, 71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.14 (1H, d, J = 16.0 Hz, C*H*CHCO$_2$), 7.42 (1H, d, J = 8.0 Hz, Ar), 7.33 (1H, s, Ar), 7.12 (1H, d, J = 8.0 Hz, Ar), 6.28 (1H, d, J = 16.0 Hz, CHC*H*CO$_2$), 5.60 (1H, s, ArC*H*), 4.23-4.16 (4H, m, OC*H*$_2$CH$_3$ and OC*H*$_2$CH$_3$), 3.98-3.89 (2H, m, OC*H*$_2$), 2.28 (3H, s, CC*H*$_3$), 2.25-2.13 (1H, m, OCH$_2$C*H*), 1.39 (1H, app. d, J = 13.5 Hz, OCH$_2$C*H*$_2$), 1.27 (3H, t, J = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 167.0, 142.4, 138.3, 134.5, 132.6, 130.6, 127.3, 127.0, 119.6, 100.4, 67.5, 60.4, 25.7, 21.2, 14.3; IR (film / cm^{-1}) ν = 2852 (O-CH-O), 1709 (C=O), 1636 (C=C), 1612 (C-O); HRMS: m/z (ES) 277.1444, $C_{16}H_{20}O_4$ [M+H]$^+$ requires 277.1440.

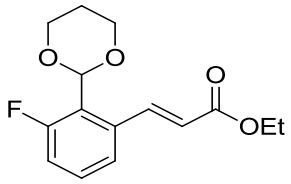
(*E*)-Ethyl 3-(2-(1,3-dioxan-2-yl)-4-(trifluoromethyl)phenyl)acrylate 276b



The title compound was prepared according to General Procedure **2** from 2-(2-bromo-5-(trifluoromethyl)phenyl)-1,3-dioxane **275b** (0.80 g, 2.6 mmol), ethyl acrylate (0.28 mL, 2.6 mmol), palladium (II) acetate (0.03 g, 0.13 mmol), tri(*o*-tolyl)phosphine (0.08 g, 0.26 mmol) and diisopropylethyl amine (1.34 mL, 7.7 mmol) in acetonitrile (25 mL). The crude product was purified by column chromatography [Petrol : EtOAc (80:20), R_f 0.48] yielding a yellow oil (0.57 g, 68 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.05 (1H, d, J = 16.0 Hz, C*H*CHCO$_2$), 7.83 (1H, app. s, Ar), 7.57-7.47 (2H, m, Ar), 6.30 (1H, d, J = 16.0 Hz, CHC*H*CO$_2$), 5.62 (1H, s, ArC*H*), 4.23-4.16 (4H, m, OC*H*$_2$CH$_2$ and OC*H*$_2$CH$_3$), 3.98-3.87 (2H, app. dd, J = 12.5 and 2.5 Hz, OC*H*$_2$CH$_2$), 2.27-2.09 (1H, m, OCH$_2$C*H*$_2$), 1.39 (1H, app. d of hep., J = 13.5 and 1.5 Hz, OCH$_2$C*H*$_2$), 1.26 (3H, t, J = 7.5 Hz, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 166.4, 140.1 (d, J = 207.0 Hz, Ar*C*HCH), 136.4 (q, J = 1.5 Hz, *C*CHCH), 132.0-130.7 (q, J = 32.5 Hz, *C*CF$_3$), 127.2, 125.8-125.7 (q, J = 3.5 Hz, *C*HCCF$_3$), 124.2-124.0 (q, J = 4.0 Hz, *C*F$_3$), 122.2, 118.4, 100.4, 99.09, 67.5, 60.7, 25.5, 14.2; IR (film / cm^{-1}) ν = 2872 (O-CH-O), 1716 (C=O), 1630 (C=C), 1580 (C-O); HRMS: m/z (ES) 331.1147, $C_{16}H_{17}O_4F_3$ [M+H]$^+$ requires 331.1157.

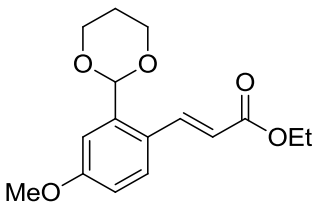
(*E*)-Ethyl 3-(2-(1,3-dioxan-2-yl)-3-fluorophenyl)acrylate 276c



The title compound was prepared according to General Procedure **2** from 2-(2-bromo-6-fluorophenyl)-1,3-dioxane **275c** (0.46 g, 1.8 mmol), ethyl acrylate (0.19 mL, 1.8 mmol), palladium (II) acetate (0.02 g, 0.09 mmol), tri(*o*-tolyl)phosphine (0.05 g, 0.18 mmol) and diisopropylethyl amine (0.92 mL, 5.3 mmol) in acetonitrile (15 mL). The crude product was purified by column chromatography [Petrol : EtOAc (80:20), R_f 0.48] yielding a yellow oil (0.40 g, 81 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.68 (1H, d, J = 16.0 Hz, ArC*H*CH), 7.35 (1H, d, J = 8.0 Hz, Ar), 7.26-7.19 (1H, m, Ar), 7.01-6.93 (1H, m, Ar), 6.24 (1H, d, J = 16.0 Hz, ArCHC*H*), 5.98 (1H, s, ArC*H*CO_2), 4.25-4.16 (4H, m, O$CH_2$$CH_2$ and O$CH_2$$CH_3$), 3.95-3.84 (2H, m, O$CH_2$$CH_2$), 2.40-2.23 (1H, m, OCH_2CH_2), 1.40 (1H, app. d of hep., J = 13.5 and 1.0 Hz, OCH_2CH_2), 1.28 (3H, t, J = 7.0 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 166.9, 160 d, J = 248.5 Hz, *C*F), 143.3 (d, J = 3.0 Hz, Ar*C*HCH), 136.3 (d, J = 3.0 Hz, *C*CHCH), 130.4 (d, J = 9.5 Hz, CFCH*C*H), 124.3 (d, J = 11.5 Hz, ArCH*C*H), 123.3 (d, J = 3.5 Hz, CF*C*C), 119.6, 116.5 (d, J = 23.5 Hz, CF*C*H), 96.3 (d, J = 10.0 Hz, Ar*C*HO_2), 68.0, 60.4, 25.9, 14.3; IR (film / cm^{-1}) ν = 2856 (O-CH-O), 1710 (C=O), 1639 (C=C), 1577 (C-O); HRMS: m/z (ES) 281.1179, $C_{15}H_{17}O_4F$ $[M+H]^+$ requires 281.1189.

(*E*)-Ethyl 3-(2-(1,3-dioxan-2-yl)-4-methoxyphenyl)acrylate 276d

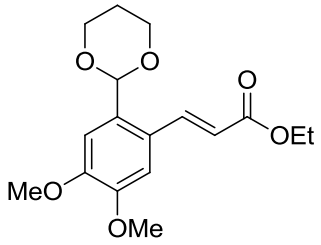


The title compound was prepared according to General Procedure **2** from 2-(2-bromo-5-methoxyphenyl)-1,3-dioxane **275d** (0.58 g, 2.1 mmol), ethyl acrylate (0.23 mL, 2.1 mmol), palladium (II) acetate (0.02 g, 0.11 mmol), tri(*o*-tolyl)phosphine (0.06 g, 0.21 mmol) and diisopropylethyl amine (1.10 mL, 6.4 mmol) in acetonitrile (15 mL). The

crude product was purified by column chromatography [Petrol : EtOAc (85:15), R_f 0.25] yielding a yellow crystalline solid (0.36 g, 58 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.04 (1H, br. d, J = 16.0 Hz, ArC*H*CH), 7.49 (1H, d, J = 8.5 Hz, Ar), 7.11 (1H, d, J = 2.5 Hz, Ar), 6.81 (1H, dd, J = 8.5 and 2.5 Hz, Ar), 6.20 (1H, br. d, J = 16.0 Hz, ArCHC*H*), 5.64 (1H, s, C*H*O), 4.26-4.14 (4H, m, OC*H*$_2$CH$_2$ and OC*H*$_2$CH$_3$), 4.01-3.90 (2H, m, OC*H*$_2$CH$_2$), 3.77 (3H, s, OC*H*$_3$), 2.31-2.12 (1H, m, OCH$_2$C*H*$_2$), 1.40 (1H, app. d of hep., J = 1.5 Hz, OCH$_2$C*H*$_2$) 1.26 (3H, t, J = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 167.7, 161.4, 141.9, 139.3, 128.6, 125.5, 117.9, 115.8, 111.9, 100.0, 67.9, 60.7, 55.8, 26.0, 14.7; IR (film / cm^{-1}) ν = 2855 (O-CH-O), 1702 (C=O), 1605 (C=C); HRMS: m/z (ES) 315.1195, $C_{16}H_{20}O_5$ [M+Na]$^+$ requires 315.1208; mp 43-44 °C.

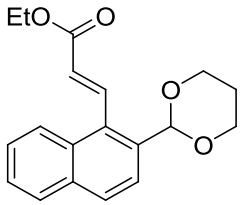
(*E*)-Ethyl 3-(2-(1,3-dioxan-2-yl)-3,4-dimethoxyphenyl)acrylate 276e



The title compound was prepared according to General Procedure **2** from 2-(2-bromo-4,5-dimethoxyphenyl)-1,3-dioxane **275e** (1.02 g, 3.4 mmol), ethyl acrylate (0.36 mL, 3.4 mmol), palladium (II) acetate (0.04 g, 0.17 mmol), tri(*o*-tolyl)phosphine (0.10 g, 0.34 mmol) and diisopropylethyl amine (1.75 mL, 10.0 mmol) in acetonitrile (40 mL). The crude product was purified by column chromatography [Petrol : EtOAc (70:30), R_f 0.49] yielding a yellow oil (0.82 g, 76 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.03 (1H, br. d, J = 16.0 Hz, ArC*H*CH), 7.11 (1H, s, Ar), 7.00 (1H, s, Ar), 6.22 (1H, br. d, J = 16.0 Hz, ArCHC*H*), 5.66 (1H, s, C*H*O), 4.26-4.15 (4H, m, OCH$_2$C*H*$_2$ and C*H*$_2$CH$_3$), 4.02-3.90 (2H, m, OC*H*$_2$CH$_2$), 3.87 (3H, s, OC*H*$_3$), 3.83 (3H, s, OC*H*$_3$), 2.33-2.10 (1H, m, OCH$_2$C*H*$_2$), 1.41 (1H, br. d, J = 13.5 Hz, OCH$_2$C*H*$_2$), 1.28 (3H, t, J = 7.0 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 167.6, 151.0, 149.5, 141.7, 131.6, 125.5, 118.1, 109.7, 109.0, 99.7, 67.9, 60.8, 56.4, 26.0, 14.8; IR (film / cm^{-1}) ν = 2853 (O-CH-O), 1703 (C=O), 1602 (C=C); HRMS: m/z (ES) 323.1495, $C_{17}H_{22}O_6$ [M+H]$^+$ requires 323.1495.

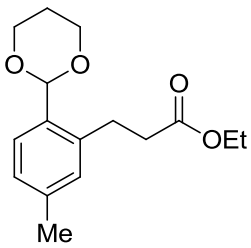
(*E*)-Ethyl 3-(2-(1,3-dioxan-2-yl)naphthalen-1-yl)acrylate 276f



The title compound was prepared according to General Procedure **2** from 2-(1-bromonaphthalen-2-yl)-1,3-dioxane **275f** (0.77 g, 2.6 mmol), ethyl acrylate (0.28 mL, 2.6 mmol), palladium (II) acetate (0.03 g, 0.13 mmol), tri(*o*-tolyl)phosphine (0.08 g, 0.26 mmol) and diisopropylethyl amine (1.37 mL, 7.8 mmol) in acetonitrile (20 mL). The crude product was purified using column chromatography [Petrol : EtOAc (85:15), R_f 0.47] yielding a yellow oil (0.69 g, 84 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.23 (1H, d, J = 16.0 Hz, ArC*H*CH), 7.96 (1H, m, Ar), 7.80-7.74 (3H, m, Ar), 7.44 (2H, m, Ar), 6.22 (1H, d, J = 16.0 Hz, ArCHC*H*), 5.66 (1H, s, ArC*H*O_2), 4.28 (2H, q, J = 7.0 Hz, OC*H*$_2$$CH_3$), 4.24-4.11 (2H, m, OC*H*$_2$$CH_2$), 3.99-3.88 (2H, dd, J = 12.0 and 2.5 Hz, OC*H*$_2$$CH_2$), 2.33-2.14 (1H, m, OCH_2C*H*$_2$), 1.39 (1H, app. d of hep., J = 13.5 and 1.5 Hz, OCH_2C*H*$_2$), 1.32 (3H, t, J= 7.0 Hz, OCH_2C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 166.4, 141.1, 134.0, 133.5, 131.2, 131.0, 129.2, 128.4, 126.7, 126.6, 126.5, 125.3, 123.6, 99.9, 67.3, 60.8, 25.7, 14.4; IR (film / cm^{-1}) ν = 2853 (O-CH-O), 1713 (C=O), 1639 (C=C), 1597 (C-O); HRMS: m/z (ES) 313.1429, $C_{19}H_{20}O_4$ $[M+H]^+$ requires 313.1440.

Ethyl 3-(2-(1,3-dioxan-2-yl)-5-methylphenyl)propanoate 277a

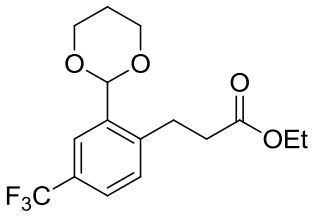


The title compound was prepared according to General Procedure **3** from (*E*)-ethyl 3-(2-(1,3-dioxan-2-yl)-5-methylphenyl)acrylate **276a** (0.64 g, 2.3 mmol), cobalt (II) chloride hexahydrate (0.05 g, 0.02 mmol) in ethanol (20 mL) with the addition of sodium

borohydride (0.17 g, 4.6 mmol). The crude product was purified using flash column chromatography [Petrol: EtOAc (80:20), R_f 0.54] yielding a colourless oil (0.44 g, 70 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.38 (1H, d, J = 8.0 Hz, CH_3CCHCH), 6.96 (1H, d, J = 8.0 Hz, CH_3CCHCH), 6.91 (1H, s, CH_2CCH), 5.54 (1H, s, $ArCHO_2$), 4.21-4.13 (2H, m, OCH_2CH_2), 4.07 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.95-3.84 (2H, m, OCH_2CH_2), 2.99-2.91 (2H, diastereotopic m., $ArCH_2CH_2$), 2.58-2.50 (2H, diastereotopic m., $ArCH_2CH_2$), 2.20 (3H, s, $ArCH_3$), 2.20-2.07 (1H, m, OCH_2CH_2), 1.35 (1H, app. d of hep., J = 1.0 Hz, OCH_2CH_2), 1.18 (3H, t, J = 7.0 Hz, CH_2CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C = 173.3, 138.6, 138.3, 133.6, 130.2, 127.2, 126.5, 100.3, 67.5, 60.3, 36.2, 27.7, 25.8, 21.2, 14.3; IR (film / cm^{-1}) ν = 2854 (O-CH-O), 1730 (C=O), 1617 (C-O); HRMS: m/z (ES) 279.1587, $C_{16}H_{22}O_4$ $[M+H]^+$ requires 279.1596.

Ethyl 3-(2-(1,3-dioxan-2-yl)-4-(trifluoromethyl)phenyl)propanoate 277b

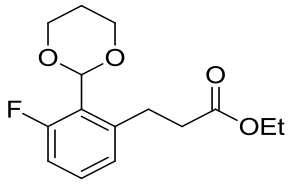


The title compound was prepared according to General Procedure **3** from (*E*)-ethyl 3-(2-(1,3-dioxan-2-yl)-4-(trifluoromethyl)phenyl)acrylate **276b** (0.32 g, 1.0 mmol), cobalt (II) chloride hexahydrate (0.002 g, 0.01 mmol) in ethanol (10 mL) with the addition of sodium borohydride (0.07 g, 1.9 mmol). The crude product was purified using flash column chromatography [Petrol: EtOAc (80:20), R_f 0.49] yielding a colourless oil (0.17 g, 54 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.25 (1H, app. dd, J = 10.0 and 2.5 Hz, Ar), 7.07 (1H, app. dd, J = 5.5 and 8.5 Hz, Ar), 6.88 (1H, app. td, J = 8.5 and 3.0 Hz, Ar), 5.54 (1H, s, CHO_2), 4.22-4.14 (2H, m, OCH_2CH_2), 4.07 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.97-3.89 (2H, m, OCH_2CH_2), 2.93 (2H, app. t, J = 8.0 Hz, OCH_2CH_2), 2.55-2.48 (2H, diastereotopic m., $ArCH_2CH_2$), 2.24-2.06 (1H, diastereotopic m., OCH_2CH_2), 1.37 (1H, app. d of hep., J = 1.5 Hz, OCH_2CH_2), 1.17 (3H, t, J = 7.0 Hz, OCH_2CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C = 172.8, 142.6, 137.3, 129.9, 128.7 (d, J = 33.0 Hz, CCF_3), 124 (d, J = 271.5 Hz, CF_3), 125.6 (q, J = 4.0 Hz, $CHCCF_3$), 123.8 (q, J = 4.0 Hz, $CHCCF_3$),

99.1, 67.4, 60.5, 53.4, 35.5, 27.5, 25.6, 14.2; IR (film / cm^{-1}) ν = 2856 (O-CH-O), 1731 (C=O), 1624 (C-O); HRMS: m/z (ES) 333.1300, $C_{16}H_{19}O_4F_3$ $[M+H]^+$ requires 333.1314.

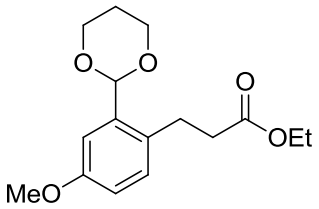
Ethyl 3-(2-(1,3-dioxan-2-yl)-3-fluorophenyl)propanoate 277c



The title compound was prepared according to General Procedure **3** from (*E*)-ethyl 3-(2-(1,3-dioxan-2-yl)-3-fluorophenyl)acrylate **276b** (0.38 g, 1.4 mmol), cobalt (II) chloride hexahydrate (0.003 g, 0.01 mmol) in ethanol (10 mL) with the addition of sodium borohydride (0.10 g, 2.7 mmol) for 72 hours. The crude product was purified using flash column chromatography [Petrol: EtOAc (75:25), R_f 0.69] yielding a colourless oil (0.19 g, 49 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.19-7.08 (1H, m, Ar), 6.93 (1H, app. d, J = 7.5 Hz, Ar), 6.87-6.76 (1H, m, Ar), 5.92 (1H, s, C*H*O_2), 4.23-4.14 (2H, m, OC*H*$_2$$CH_2$), 4.08 (2H, q, J = 7.0 Hz, OC*H*$_2$$CH_3$), 3.89 (2H, app. td, J = 12.0 and 2.0 Hz, OC*H*$_2$$CH_2$), 3.33-3.28 (2H, diastereotopic m., ArC*H*$_2$$CH_2$), 2.64-2.54 (2H, diastereotopic m., $ArCH_2$C*H*$_2$), 2.31-2.10 (1H, diastereotopic m., OCH_2C*H*$_2$), 1.37 (1H, app. d of hep., J = 1.5 Hz, OCH_2C*H*$_2$), 1.20 (3H, t, J = 7.0 Hz, OCH_2C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 173.4, 160 d, J = 247.5 Hz, *C*F), 143.0 (d, J = 2.0 Hz, *C*CH_2), 130.2 (d, J = 9.5 Hz, CFCH*C*H), 126.5 (d, J = 3.5 Hz, CFCHCH*C*H), 123.8 (d, J = 10.5 Hz, CF*C*CHO_2), 113.4 (d, J = 23.5 Hz, *C*HCF), 97.0 (d, J = 10.0 Hz, *C*HO_2), 67.7, 60.3, 36.6, 28.6 (d, J = 2.0 Hz, Ar*C*H_2), 25.8, 14.3; IR (film / cm^{-1}) ν = 2856 (O-CH-O), 1729 (C=O), 1619 (C-O); HRMS: m/z (ES) 283.1351, $C_{15}H_{19}O_4F$ $[M+H]^+$ requires 283.1346.

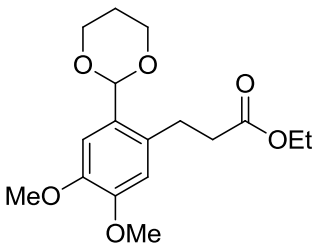
Ethyl 3-(2-(1,3-dioxan-2-yl)-4-methoxyphenyl)propanoate 277d



The title compound was prepared according to General Procedure **3** from ethyl 3-(2-(1,3-dioxan-2-yl)-4-methoxyphenyl)acrylate **276d** (0.36 g, 1.2 mmol), cobalt (II) chloride hexahydrate (0.003 g, 0.01 mmol) in ethanol (10 mL) with the addition of sodium borohydride (0.09 g, 2.4 mmol) for 48 hours. The crude product was purified using flash column chromatography [Petrol: EtOAc (80:20), R_f 0.44] yielding a colourless oil (0.26 g, 71 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.08 (1H, d, J = 3.0 Hz, Ar), 7.01 (1H, br. d, J = 8.5 Hz, Ar), 6.73 (1H, dd, J = 8.5 and 3.0 Hz, Ar), 5.55 (1H, s, ArC*H*O_2), 4.18 (2H, dd, J = 11.0 and 5.0 Hz, OC*H*$_2$$CH_2$), 4.06 (2H, q, J = 7.5 Hz, OC*H*$_2$$CH_3$), 3.91 (2H, td, J = 12.5 and 2.0 Hz, OC*H*$_2$$CH_2$), 3.71 (3H, s, OC*H*$_3$), 2.91 (2H, t, J = 8.0 Hz, ArCH_2C*H*$_2$), 2.50 (2H, t, J = 7.5 Hz, ArC*H*$_2$$CH_2$), 2.16 (1H, m, OCH_2C*H*$_2$), 1.36 (1H, m, OCH_2C*H*$_2$), 1.17 (3H, t, J = 7.0 Hz, OCH_2C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C =173.7, 158.6, 137.8, 131.0, 130.8, 115.6, 111.6, 100.2, 67.8, 60.7, 55.7, 36.7, 27.4, 26.1, 14.6; IR (film / cm^{-1}) ν = 2852 (O-CH-O), 1729 (C=O); HRMS: m/z (ES) 295.1551, $C_{16}H_{22}O_5$ $[M+H]^+$ requires 295.1545.

Ethyl 3-(2-(1,3-dioxan-2-yl)-3,4-dimethoxyphenyl)propanoate 277e

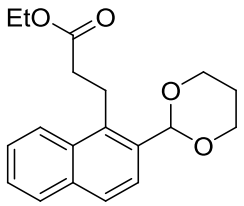


The title compound was prepared according to General Procedure **3** from ethyl 3-(2-(1,3-dioxan-2-yl)-4,5-dimethoxyphenyl)acrylate **276e** (0.82 g, 2.6 mmol), cobalt (II) chloride hexahydrate (0.01 g, 0.03 mmol) in ethanol (20 mL) with the addition of sodium borohydride (0.19 g, 5.1 mmol) for 48 hours. The crude product was purified using flash

column chromatography [Petrol: EtOAc (80:20), R_f 0.11] yielding a pale yellow crystalline solid (0.73 g, 87 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.07 (1H, s, Ar), 6.61 (1H, s, Ar), 5.54 (1H, s, C*H*O_2), 4.19 (2H, dd, J = 12.0 and 5.0 Hz, OC*H*$_2$$CH_2$), 4.08 (2H, q, J = 7.0 Hz, OC*H*$_2$$CH_3$), 3.92 (2H, td, J = 12.5 and 2.5 Hz, OC*H*$_2$$CH_2$), 3.82 (3H, s, OC*H*$_3$), 3.78 (3H, s, OC*H*$_3$), 2.95-2.87 (2H, m, ArC*H*$_2$$CH_2$), 2.56-2.49 (2H, m, Ar$CH_2$C*H*$_2$), 2.26-2.09 (1H, m, OCH_2C*H*$_2$), 1.37 (1H, app. d of hep., J = 13.5 and 1.5 Hz, OCH_2C*H*$_2$), 1.19 (3H, t, J = 7.0 Hz, OCH_2C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 173.6, 149.4, 147.8, 131.3, 129.2, 112.8, 109.8, 100.1, 67.9, 60.8, 56.3, 36.8, 27.8, 26.1, 14.6; IR (film / cm^{-1}) ν = 2858 (O-CH-O), 1729 (C=O); HRMS: m/z (ES) 325.1667, $C_{17}H_{25}O_6$ $[M+H]^+$ requires 325.1651; mp 58-60 °C.

Ethyl 3-(2-(1,3-dioxan-2-yl)naphthalen-1-yl)propanoate 277f

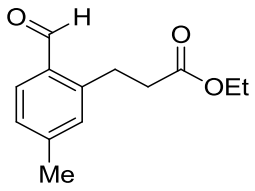


The title compound was prepared according to General Procedure **3** from (*E*)-ethyl 3-(2-(1,3-dioxan-2-yl)naphthalen-1-yl)acrylate **276f** (1.31 g, 4.2 mmol), cobalt (II) chloride hexahydrate (0.01 g, 0.04 mmol) in ethanol (40 mL) with the addition of sodium borohydride (0.32 g, 8.4 mmol) for 96 hours. The crude product was purified using flash column chromatography [Petrol: EtOAc (75:25), R_f 0.51] yielding a colourless oil (0.75 g, 75 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.01 (1H, d, J = 8.5 Hz, Ar), 7.81-7.72 (1H, m, Ar), 7.69 (2H, s, Ar), 7.43 (2H, app. pent. of d, J = 1.5 and 8.0 Hz, Ar), 5.82 (1H, s, C*H*O_2), 4.23 (2H, app dd, J = 5.0 and 11.0 Hz, OC*H*$_2$$CH_2$), 4.13 (2H, q, J= 7.0 Hz, OC*H*$_2$$CH_3$), 3.99 (2H, td, J = 12.0 and 2.0 Hz, OC*H*$_2$$CH_2$), 3.50-3.42 (2H, diastereotopic m., ArC*H*$_2$$CH_2$), 2.67-2.58 (2H, diastereotopic m., ArCH_2C*H*$_2$), 2.31-2.14 (1H, diastereotopic m., OCH_2C*H*$_2$), 1.41 (1H, d, J = 13.5 Hz, OCH_2C*H*$_2$), 1.22 (3H, t, J = 7.0 Hz, OCH_2C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 173.4, 134.6, 134.0, 133.9, 131.7, 128.8, 127.2, 126.3, 125.9, 124.0, 100.5, 67.6, 60.5, 35.6, 25.8, 23.5, 14.3; IR (film / cm^{-1}) ν = 2854

(O-CH-O), 1727 (C=O), 1600 (C-O); HRMS: m/z (ES) 315.1581, $C_{19}H_{22}O_4$ $[M+H]^+$ requires 315.1596.

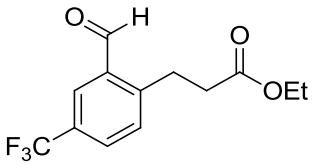
Ethyl 3-(2-formyl-5-methylphenyl)propanoate 278a



The title compound was prepared according to General Procedure **4** from ethyl 3-(2-(1,3-dioxan-2-yl)-5-methylphenyl)propanoate **277a** (0.26 g, 1.0 mmol), which was added to a solution of acetic acid : water (14 mL : 6 mL) and stirred open to the air overnight. The product was obtained as a white crystalline solid (0.16 g, 73 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.07 (1H, s, C*H*O), 7.63 (1H, d, J = 8.0 Hz, C*H*CCOH), 7.14 (1H, br. d, J = 8.0 Hz, C*H*CCH$_3$), 7.06 (1H, br. s, C*H*CCH$_3$), 4.04 (2H, q, J = 7.0 Hz, OC*H*$_2$CH$_3$), 3.24 (2H, app. t, J = 8.0 Hz, ArC*H*$_2$CH$_2$), 2.55 (2H, app. t, J = 8.0 Hz, ArCH$_2$C*H*$_2$), 2.32 (3H, s, ArC*H*$_3$), 1.15 (3H, t, J = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 192.3, 172.8, 144.9, 142.9, 133.9, 132.0, 131.5, 127.8, 60.5, 35.6, 28.1, 21.8, 14.2; IR (film / cm^{-1}) ν = 1729 (C=O), 1690 (C=O), 1610 (C-O); HRMS: m/z (ES) 243.0989, $C_{13}H_{16}O_3$ $[M+Na]^+$ requires 243.0997, mp 37-39 °C.

Ethyl 3-(2-formyl-4-(trifluoromethyl)phenyl)propanoate 278b

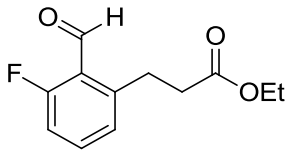


The title compound was prepared according to General Procedure **4** from ethyl 3-(2-(1,3-dioxan-2-yl)-4-(trifluoromethyl)phenyl)propanoate **277b** (0.15 g, 0.46 mmol), which was added to a solution of acetic acid : water (14 mL : 6 mL) and stirred open to the air for 36 hours. The product was obtained as a colourless oil (0.09 g, 69 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.21 (1H, s, C*H*O), 8.01 (1H, br. s, C*H*CCHO), 7.69 (1H, dd, J = 8.0 and 1.5 Hz, CC*H*CH), 7.43 (1H, d, J = 8.0 Hz, C*H*CCH$_2$), 4.05 (2H, q, J = 7.0 Hz, OC*H*$_2$CH$_3$), 3.34 (2H, t, J = 7.5 Hz, ArC*H*$_2$CH$_2$), 2.60 (2H, t, J = 7.5 Hz,

$ArCH_2CH_2$), 1.15 (3H, t, J = 7.0 Hz, OCH_2CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C = 191.1, 172.2, 146.8, 134.1, 132.0, 130.1, 130.0, 129.7, 60.7, 35.2, 27.8, 14.2; IR (film / cm^{-1}) ν = 1731 (C=O), 1704 (C=O), 1618 (C-O); HRMS: m/z (ES) 275.0868, $C_{13}H_{13}O_3F_3$ $[M+H]^+$ requires 275.0895.

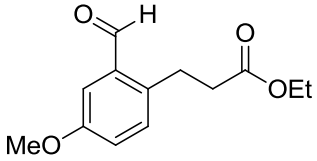
Ethyl 3-(3-fluoro-2-formylphenyl)propanoate 278c



The title compound was prepared according to General Procedure **4** from ethyl 3-(2-(1,3-dioxan-2-yl)-3-fluorophenyl)propanoate **277c** (0.19 g, 0.68 mmol), which was added to a solution of acetic acid : water (7 mL : 3 mL) and stirred open to the air overnight. The product was obtained as a colourless oil (0.12 g, 79 %).

^1H NMR (300 MHz, $CDCl_3$): δ_H = 10.46 (1H, s, C*H*O), 7.41 (1H, td, J = 8.0 and 6.0 Hz, Ar), 7.07-6.94 (2H, m, Ar), 4.04 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.23 (2H, t, J = 7.5 Hz, $ArCH_2$), 2.55 (2H, t, J = 7.5 Hz, $ArCH_2CH_2$), 1.15 (3H, t, J = 7.0 Hz, OCH_2CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C = 189.0 (d, J = 11.0 Hz, *C*HO), 172.8, 166.64 (d, J = 257.5 Hz, *C*F), 144.7, 135.40 (d, J = 10.5 Hz, CFCH*C*H), 127.2 (d, J = 3.5 Hz, CH_2CCH), 122.19 (d, J = 5.5 Hz, CF*C*), 114.6 (d, J = 22.0 Hz, CF*C*H), 60.5, 35.0, 29.03 (d, J = 2.0 Hz, $ArCH_2$), 14.2; IR (film / cm^{-1}) ν = 1730 (C=O), 1695 (C=O), 1610 (C-O).

Ethyl 3-(2-formyl-4-methoxyphenyl)propanoate 278d

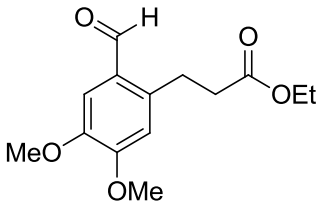


The title compound was prepared according to General Procedure **4** from ethyl-3-(2-(1,3-dioxan-2-yl)-4-methoxyphenyl)propanoate **277d** (0.15 g, 0.5 mmol), which was added to a solution of acetic acid : water (14 mL : 6 mL) and stirred open to the air overnight. The product was obtained as an orange oil (0.12 g, 86 %).

^1H NMR (300 MHz, $CDCl_3$): δ_H = 10.16 (1H, s, C*H*O), 7.27 (1H, d, J = 2.5 Hz, Ar), 7.19 (1H, d, J = 5.0 Hz, Ar), 6.99 (1H, dd, J = 8.5 and 3.0 Hz, Ar), 4.04 (2H, q, J = 7.0 Hz,

OC*H*$_2$CH$_3$), 3.78 (3H, s, OC*H*$_3$), 3.21 (2H, t, J = 7.5 Hz, ArC*H*$_2$CH$_2$), 2.51 (2H, t, J = 7.5 Hz, ArCH$_2$C*H*$_2$) 1.15 (3H, t, J = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$): δ_C = 192.3, 173.0, 158.9, 135.7, 134.9, 132.7, 120.9, 116.2, 60.9, 55.9, 36.5, 27.2, 14.6; IR (film / cm^{-1}) ν = 1728 (C=O), 1686 (C=O); HRMS: m/z (ES) 259.0941, $C_{13}H_{16}O_4$ $[M+Na]^+$ requires 259.0946.

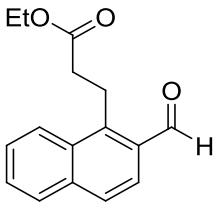
Ethyl 3-(2-formyl-3,4-dimethoxyphenyl)propanoate 278e



The title compound was prepared according to General Procedure **4** from ethyl-3-(2-(1,3-dioxan-2-yl)-4,5-dimethoxyphenyl)propanoate **277e** (0.47 g, 1.5 mmol), which was added to a solution of acetic acid : water (14 mL : 6 mL) and stirred open to the air overnight. The product was obtained as a white solid (0.30 g, 77 %).

^{1}H NMR (300 MHz, CDCl$_3$): δ_H = 10.10 (1H, s, C*H*O), 7.28 (1H, s, Ar), 6.71 (1H,s, Ar), 4.05 (2H, q, J = 7.0 Hz, OC*H*$_2$CH$_3$), 3.88 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 3.24 (2H, t, J = 7.5 Hz, ArC*H*$_2$CH$_2$), 2.57 (2H, t, J = 7.5 Hz, ArCH$_2$C*H*$_2$), 1.16 (3H, t, J = 7.5 Hz, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$): δ_C = 190.4, 172.9, 154.1, 148.3, 138.7, 127.1, 113.5, 112.9, 61.0, 56.5, 56.4, 36.8, 27.4, 14.6; IR (film / cm^{-1}) ν = 1727 (C=O), 1673 (C=O); HRMS: m/z (ES) 289.1035, $C_{14}H_{18}O_5$ $[M+Na]^+$ requires 289.1052; mp 121-123 °C.

Ethyl 3-(2-formylnaphthalen-1-yl)propanoate 278f

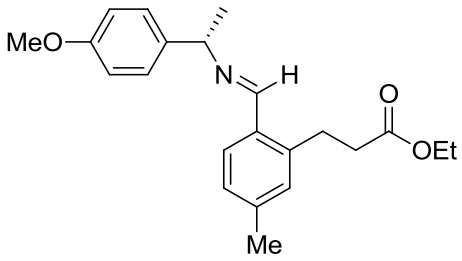


The title compound was prepared according to General Procedure **4** from ethyl 3-(2-(1,3-dioxan-2-yl)naphthalen-1-yl)propanoate **277f** (0.25 g, 0.80 mmol), which was

added to a solution of acetic acid : water (14 mL : 6 mL) and stirred open to the air overnight. The product was obtained as a yellow oil (0.14 g, 71 %).

^{1}H NMR (300 MHz, $CDCl_3$): 10.53 (1H, s, C*H*O), 8.20-8.13 (1H, m, Ar), 7.88-7.72 (3H, m, Ar), 7.59-7.51 (2H, m, Ar), 4.08 (2H, q, J= 7.0 Hz, OCH_2CH$_3$), 3.80 (2H, t, J= 8.0 Hz, ArCH_2CH$_2$), 2.70-2.63 (2H, diastereotopic m., ArCH$_2$CH_2), 1.16 (3H, t, J= 7.0 Hz, OCH$_2$CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 192.0, 172.4, 142.2, 136.3, 131.7, 131.0, 129.1, 128.7, 127.7, 127.3, 125.0, 124.8, 60.8, 35.8, 22.0, 14.2; IR (film / cm^{-1}) ν = 1727 (C=O), 1681 (C=O), 1619 (C-O); HRMS: m/z (ES) 257.1185, $C_{16}H_{16}O_3$ [M+Na]$^+$ requires 257.1178.

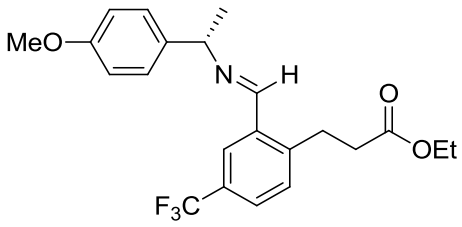
(*S,E*)-Ethyl3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)-5-methylphenyl) propanoate 279a



Ethyl 3-(2-formyl-5-methylphenyl)propanoate **278a** (0.07 g, 0.30 mmol) was dissolved in dry CH_2Cl_2 (15 mL) with $MgSO_4$ and stirred under a nitrogen atmosphere. After 5 minutes, (*S*)-(-)-4-methoxy-α-methylbenzylamine (0.04 mL, 0.30 mmol) was added and the solution was stirred for 5 hours. The solution was then filtered and the solvent evaporated under reduced pressure, yielding a hygroscopic white solid (0.10 g, 82 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.45 (1H, s, ArC*H*N), 7.61 (1H, d, J = 8.0 Hz, Ar), 7.31-7.24 (2H, m, Ar), 7.02-6.93 (2H, m, Ar), 6.84 -6.77 (2H, m, Ar), 4.39 (1H, q, J = 4.5 Hz, C*H*CH$_3$), 4.06 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 3.72 (3H, s, OCH_3), 3.14 (2H, t, J = 8.5 Hz, ArCH_2CH$_2$), 2.51 (2H, t, J = 8.0 Hz, ArCH$_2$CH_2), 2.26 (3H, s, ArCH_3), 1.48 (3H, d, J = 6.5 Hz, CHCH_3), 1.17 (3H, t, J =7.0 Hz, OCH$_2$CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 173.0, 158.4, 157.9, 140.3, 140.2, 137.7, 131.4, 131.0, 129.7, 127.6, 127.5, 126.9, 113.9, 113.8, 70.1, 60.4, 55.3, 36.0, 28.5, 25.3, 21.4, 14.3; HRMS: m/z (ES) 354.2071, $C_{22}H_{27}O_3N$ [M+H]$^+$ requires 354.2069.

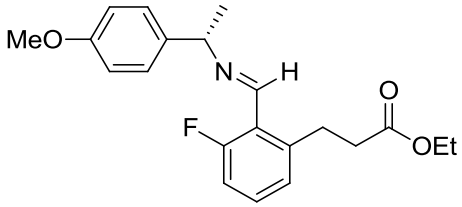
(*S*,*E*)-Ethyl 3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)-4-(trifluoromethyl)phenyl)propanoate 279b



Ethyl 3-(2-formyl-4-(trifluoromethyl)phenyl)propanoate **278b** (0.11 g, 0.39 mmol) was dissolved in dry CH_2Cl_2 (20 mL) with $MgSO_4$ and stirred under a nitrogen atmosphere. After 5 minutes, (*S*)-(-)-4-methoxy-α-methylbenzylamine (0.06 mL, 0.39 mmol) was added and the solution was stirred for 5 hours. The solution was then filtered and the solvent evaporated under reduced pressure, yielding a yellow oil (0.14 g, 85 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.55 (1H, s, ArC*H*N), 8.01 (1H, s, C*H*CCHN), 7.48 (1H, app. dd, J = 8.0 and 1.5 Hz, Ar), 7.30-7.23 (3H, m, Ar), 6.85-6.78 (2H, m, Ar), 4.46 (1H, q, J = 6.5 Hz, C*H*CH_3), 4.06 (2H, q, J = 7.0 Hz), 3.73 (3H, s, OC*H*$_3$), 3.20 (2H, t, J = 8.0 Hz, ArC*H*$_2$$CH_2$), 2.57-2.50 (2H, diastereotopic m., $ArCH_2$C*H*$_2$), 1.51 (3H, d, J = 6.5 Hz, CHC*H*$_3$), 1.16 (3H, t, J = 7.0 Hz, OCH_2C*H*$_3$); HRMS: m/z (ES) 408.1802, $C_{22}H_{24}O_3NF_3$ $[M+H]^+$ requires 408.1787.

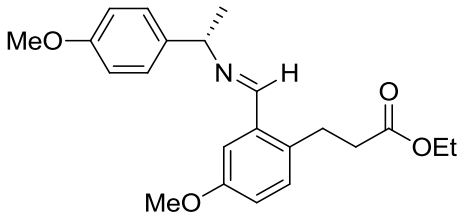
(*S*,*E*)-Ethyl-3-(3-fluoro-2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)propanoate 279c



Ethyl 3-(3-fluoro-2-formylphenyl)propanoate **278c** (0.06 g, 0.27 mmol) was dissolved in dry CH_2Cl_2 (15 mL) with $MgSO_4$ and stirred under a nitrogen atmosphere. After 5 minutes, (*S*)-(-)-4-methoxy-α-methylbenzylamine (0.04 mL, 0.27 mmol) was added and the solution was stirred for 5 hours. The solution was then filtered and the solvent evaporated under reduced pressure, yielding a yellow oil (0.08 g, 82 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.65 (1H, s, ArC*H*N), 7.35-7.15 (2H, m, Ar), 7.02-6.72 (5H, m, Ar), 4.38 (1H, q, J = 6.5 Hz, C*H*CH_3), 4.06 (2H, q, J = 7.0 Hz, OC*H*$_2CH_3$), 3.72 (3H, s, OC*H*$_3$), 3.26 (2H, t, J = 8.0 Hz, ArC*H*$_2CH_2$), 2.55 (2H, t, J = 8.0 Hz, ArCH_2C*H*$_2$), 1.49 (3H, d, J = 6.5 Hz, CHC*H*$_3$), 1.17 (3H, t, J = 7.0 Hz, OCH_2C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 173.3, 158.5, 153.4, 143.2, 137.4, 130.9, 130.8, 127.6, 127.3, 126.7, 122.5, 113.8, 113.5, 71.4, 60.3, 55.3, 35.6, 29.7, 25.6, 14.3; HRMS: m/z (ES) 258.1815, $C_{21}H_{24}O_3NF$ $[M+H]^+$ requires 358.1818.

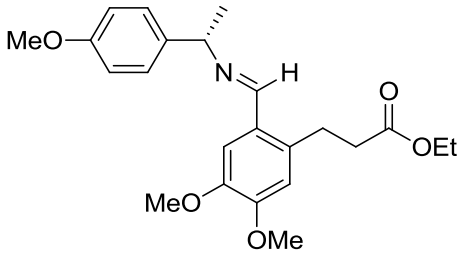
(*S,E*)-Ethyl-3-(4-methoxy-2((1-(4methoxyphenyl)ethylimino)methyl)phenyl)-propaneate 279d



Ethyl-3-(2-formyl-4-methoxyphenyl)propanoate **278d** (0.18 g, 0.75 mmol) was dissolved in dry CH_2Cl_2 (20 mL) with $MgSO_4$ and stirred under a nitrogen atmosphere. After 5 minutes, (*S*)-(-)-4-methoxy-α-methylbenzylamine (0.11 mL, 0.75 mmol) was added and the solution was stirred for 5 hours. The solution was then filtered and the solvent evaporated under reduced pressure, yielding a yellow oil (0.23 g, 85 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.50 (1H, s, ArC*H*N), 7.34-7.24 (3H, m, Ar), 7.04 (1H, d, J = 8.5 Hz, Ar), 6.82-6.76 (3H, m, Ar), 4.42 (1H, q, J = 6.5 Hz, C*H*CH_3), 4.03 (2H, q, J = 7.0 Hz, OC*H*$_2CH_3$), 3.72 (3H, s, OC*H*$_3$), 3.70 (3H, s, OC*H*$_3$), 3.07 (2H, br. t, J = 7.5 Hz, ArC*H*$_2CH_2$), 2.47 (2H, t, J = 7.5 Hz, ArCH_2C*H*$_2$), 1.48 (3H, d, J = 6.5 Hz, CHC*H*$_3$), 1.15 (3H, t, J = 7.0 Hz, OCH_2C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 172.9, 158.5, 158.3, 157.5, 137.4, 135.0, 132.7, 131.3, 127.7, 116.7, 114.1, 113.8, 113.2, 69.9, 60.4, 55.4, 55.3, 36.3, 29.7, 27.5, 25.2, 14.3; HRMS: m/z (ES) 370.2021, $C_{22}H_{27}O_4N$ $[M+H]^+$ requires 370.2018.

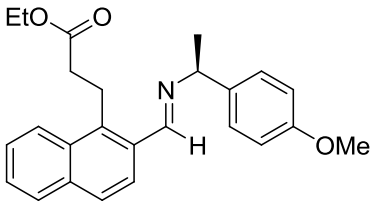
(*S*,*E*)-Ethyl-3-(3,4-dimethoxy-2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl) propanoate 279e



Ethyl 3-(2-formyl-3,4-dimethoxyphenyl)propanoate **278e** (0.49 g, 1.9 mmol) was dissolved in dry CH_2Cl_2 (35 mL) with $MgSO_4$ and stirred under a nitrogen atmosphere. After 5 minutes, (*S*)-(-)-4-methoxy-α-methylbenzylamine (0.28 mL, 1.9 mmol) was added and the solution was stirred for 5 hours. The solution was then filtered and the solvent evaporated under reduced pressure, yielding a yellow oil (0.68 g, 93 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.60 (1H, s, ArC*H*N), 7.53 (1H, br. s, Ar), 7.42-7.38 (2H, m, Ar), 6.96-6.91 (2H, m, Ar), 6.74 (1H, s, Ar), 4.55 (1H, q, J = 6.5 Hz, C*H*CH_3), 4.18 (2H, q, J = 7.0 Hz, C*H*$_2$$CH_3$), 3.97 (3H, s, OC*H*$_3$), 3.94 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 3.19 (2H, t, J = 8.0 Hz, ArC*H*$_2$$CH_2$), 2.64-2.59 (2H, diastereotopic m., $ArCH_2$C*H*$_2$), 1.62 (3H, d, J = 6.5 Hz, CHC*H*$_3$), 1.29 (3H, t, J = 7.0 Hz, OCH_2C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 172.8, 158.5, 156.7, 150.7, 147.7, 137.6, 133.9, 127.7, 126.5, 113.8, 112.6, 110.7, 69.6, 60.5, 56.0, 55.9, 55.3, 36.5, 27.6, 25.1, 14.3; HRMS: m/z (ES) 400.2143, $C_{23}H_{30}O_5N$ $[M+H]^+$ requires 400.2124.

(*S*,*E*)-Ethyl-3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)naphthalen-1-yl)propanoate 279f

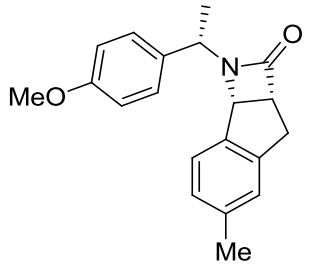


Ethyl 3-(2-(1,3-dioxan-2-yl)naphthalen-1-yl)propanoate **278e** (0.04 g, 0.16 mmol) was dissolved in dry CH_2Cl_2 (10 mL) with $MgSO_4$ and stirred under a nitrogen atmosphere. After 5 minutes, (*S*)-(-)-4-methoxy-α-methylbenzylamine (0.02 mL, 0.16 mmol) was

added and the solution was stirred for 5 hours. The solution was then filtered and the solvent evaporated under reduced pressure, yielding a yellow oil (0.068 g, 92 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.97 (1H, s, ArC*H*N), 8.19 (1H, d, J= 8.5 Hz, C*H*CCHN), 8.14 (1H, d, J= 9.0 Hz, Ar), 7.90 (1H, d, J= 8.0 Hz, Ar), 7.79 (1H, d, J= 8.5 Hz, Ar), 7.59 (2H, d J= 8.0 Hz, Ar), 7.46 (2H, d, J= 8.5 Hz, Ar), 6.96 (2H, d, J= 8.5 Hz, Ar), 4.66 (1H, q, J= 6.5 Hz, C*H*CH_3), 4.23 (1H, q, J= 7.5 Hz, OC*H*$_2$$CH_3$), 3.86 (3H, s, OC*H*$_3$), 3.73 (2H, t, J= 7.5 Hz, ArC*H*$_2$$CH_2$), 2.74 (2H, t, J= 8.0 Hz, ArCH_2C*H*$_2$), 1.68 (3H, d, J= 6.5 Hz, CHC*H*$_3$), 1.31 (3H, t, J= 7.5 Hz, OCH_2C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 172.9, 158.5, 157.7, 137.5, 137.0, 134.7, 131.8, 131.5, 128.9, 127.7, 127.2, 126.7, 126.6, 125.3, 124.0, 114.1, 113.9, 70.0, 60.7, 55.3, 35.6, 25.2, 22.8, 14.3; HRMS: m/z (ES) 390.2053, $C_{25}H_{27}O_3N$ $[M+H]^+$ requires 390.2069.

(2a*R*,7b*R*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-5-methyl-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one 280a

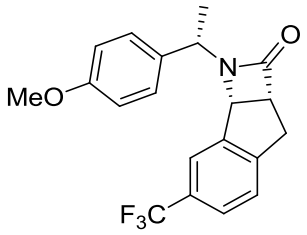


The title compound was prepared according to General Procedure **5** from (*S,E*)-ethyl 3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)-5-methylphenyl)propanoate **279a** (0.087 g, 0.25 mmol), which was dissolved in THF (7 mL) under a nitrogen atmosphere. 15-Crown-5 (0.05 mL, 0.27 mmol) and NaHMDS (1M in THF, 0.27 mL, 0.27 mmol) were added and the mixture was stirred for 8 hours at -40 °C and allowed to warm to room temperature. The crude product was purified using flash column chromatography [Petrol : EtOAc (60:40), R_f 0.35] yielding a white crystalline solid (0.045 g, 60 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.34-7.29 (2H, m, Ar), 7.11 (1H, s, Ar), 7.06 (1H, d, J = 8.0 Hz, Ar), 7.02-6.98 (1H, m, Ar), 6.98-6.95 (2H, m, Ar), 5.00 (1H, q, J = 7.0 Hz, C*H*CH_3), 4.86 (1H, d, J = 4.5 Hz, CHC*H*N), 3.91-3.86 (4H, m, C*H*CH_2 and OC*H*$_3$), 3.36 (1H, d, J = 17.5 Hz, CHC*H*$_2$), 2.99 (1H, dd, J = 17.5 and 10.5 Hz, CHC*H*$_2$), 2.38 (3H, s, ArC*H*$_3$), 1.44 (3H, d, J = 7.0 Hz, CHC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 169.9,

159.0, 145.4, 138.8, 136.9, 132.1, 128.4, 127.4, 126.9, 125.9, 114.0, 61.1, 55.4, 51.9, 50.9, 29.9, 21.4, 18.9; IR (film / cm^{-1}) ν = 1738 (C=O); HRMS: m/z (ES) 208.1642, $C_{20}H_{21}O_2N$ $[M+H]^+$ requires 308.1651; mp 71-73 °C; $[\propto]_D^{25}$ = -18 (*c* 0.895, $CHCl_3$).

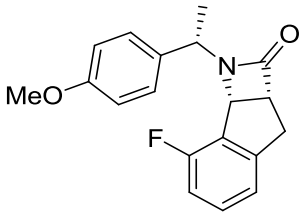
(2a*R*,7b*R*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-6-(trifluoromethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one 280b



The title compound was prepared according to General Procedure **5** from (*S,E*)-ethyl 3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)-4-(trifluoromethyl)phenyl)propanoate **279b** (0.086 g, 0.21 mmol), which was dissolved in THF (6 mL) under a nitrogen atmosphere. 15-Crown-5 (0.05 mL, 0.23 mmol) and NaHMDS (1M in THF, 0.23 mL, 0.23 mmol) were added and the mixture was stirred for 8 hours at -40 °C and allowed to warm to room temperature. The crude product was purified using flash column chromatography [Petrol : EtOAc (60:40), R_f 0.24] yielding a white crystalline solid (0.053 g, 69 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.53 (1H, d, J = 7.5 Hz, Ar), 7.39 (1H, d, J = 8.0 Hz, Ar), 7.24 (2H, d, J = 8.5 Hz, Ar), 7.14 (1H, s, Ar), 6.92 (2H, d, J = 8.5 Hz, Ar), 4.89 (1H, q, J = 7.0 Hz, C*H*CH_3), 4.84 (1H, d, J = 4.0 Hz, NC*H*CH), 3.96 (1H, dq, J = 10.5 and 2.0 Hz, C*H*CH_2), 3.87 (3H, s, OC*H*$_3$), 3.45 (1H, d, J = 18.0 Hz, CHC*H*$_2$), 3.08 (1H, dd, J = 17.5 and 10.5 Hz, CHC*H*$_2$), 1.51 (3H, d, J = 7.0 Hz, CHC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 169.3, 159.3, 149.1, 140.4, 131.7, 128.7 (q, J = 31.0 Hz, CF_3C), 128.4, 126.7, 125.8 (q, J = 4.0 Hz, CHC*C*H), 124.1 (q, J = 273.0 Hz, *C*F_3), 123.2 (q, J = 4.0 Hz, *C*F_3CCH), 122.7, 114.1, 61.2, 55.3, 52.8, 51.7, 30.2, 19.3; IR (film / cm^{-1}) ν = 1742 (C=O); HRMS: m/z (ES) 362.1358, $C_{20}H_{18}O_2NF_3$ $[M+H]^+$ requires 362.1368; mp 108-110 °C; $[\propto]_D^{25}$ = -14 (*c* 0.5825, $CHCl_3$).

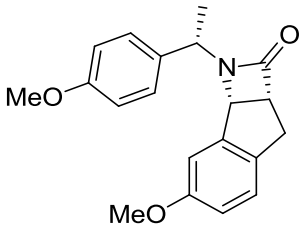
(2a*R*,7b*R*)-7-Fluoro-1-((*S*)-1-(4-methoxyphenyl)ethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one 280c



The title compound was prepared according to General Procedure **5** from (*S,E*)-ethyl 3-(3-fluoro-2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)propanoate **279c** (0.070 g, 0.20 mmol), which was dissolved in THF (6 mL) under a nitrogen atmosphere. 15-Crown-5 (0.04 mL, 0.22 mmol) and NaHMDS (1M in THF, 0.22 mL, 0.22 mmol) were added and the mixture was stirred for 8 hours at -40 °C and allowed to warm to room temperature. The crude product was purified using flash column chromatography [Petrol : EtOAc (60:40), R_f 0.30] yielding a white crystalline solid (0.048 g, 79 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.37-7.26 (3H, m, Ar), 7.08 (1H, s, Ar), 6.94-6.86 (3H, m, Ar), 5.02-4.95 (2H, m, NC*H*CH and C*H*CH_3), 3.98-3.92 (1H, m, C*H*CH_2), 3.85 (3H, s, OC*H*$_3$), 3.44 (1H, d, J = 17.5 Hz, CHC*H*$_2$), 3.05 (1H, dd, J = 18.0 and 11.0 Hz, CHC*H*$_2$), 1.51 (3H, d, J = 7.0 Hz, CHC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 169.2, 163.2 (d, J = 247 Hz, *C*F), 158.9, 148.7 (d, J = 4.5 Hz, CH_2*C*), 132.6, 131.1 (d, J = 7.5 Hz, CF*C*CH), 128.2 (d, J = 1.0 Hz, CFCH*C*H), 127.2, 127.0, 122.0 (d, J = 3.5 Hz, CFCHCH*C*H), 113.9, 113.2 (d, J = 20.5 Hz, CF*C*H), 57.7, 55.3, 52.5, 51.4, 30.2, 18.2 (d, J = 3.5Hz); IR (film / cm^{-1}) ν = 1743 (C=O); HRMS: m/z (ES) 334.1225, $C_{19}H_{18}O_2NF$ $[M+Na]^+$ requires 334.1219; mp 75-77 °C; $[\propto]_D^{25}$ = -46 (*c* 0.5475, $CHCl_3$).

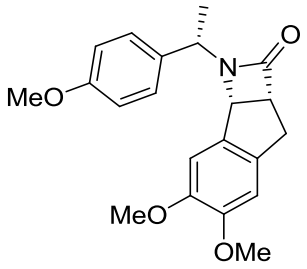
(2a*R*,7b*R*)-6-Methoxy-1-((*S*)-1-(4-methoxyphenyl)ethyl)-2a,3-dihydro-1H-indeno [1,2-b]azet-2-(7bH)-one 280d



The title compound was prepared according to General Procedure **5** from (*S,E*)-ethyl 3-(4-methoxy-2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)propanoate **279d** (0.105 g, 0.28 mmol), which was dissolved in THF (7 mL) under a nitrogen atmosphere. 15-Crown-5 (0.06 mL, 0.31 mmol) and NaHMDS (1M in THF, 0.31 mL, 0.31 mmol) were added and the mixture was stirred for 8 hours at -40 °C and allowed to warm to room temperature. The crude product was purified using flash column chromatography [Petrol : EtOAc (60:40), R_f 0.25] yielding a white crystalline solid (0.057 g, 62 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.30 (2H, d, J = 8.0 Hz, Ar), 7.19 (1H, d, J = 8.5 Hz, Ar), 6.98-6.94 (2H, m, Ar), 6.86 (1H, dd, J = 8.0 and 2.5 Hz, Ar), 6.60 (1H, d, J = 2.5 Hz, Ar), 4.98 (1H, q, J = 7.0 Hz, C*H*CH_3), 4.77 (1H, d, J = 4.5 Hz, NC*H*CH), 3.91 (1H, dq, J = 10.5 and 2.5 Hz, C*H*CH_2), 3.88 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.33 (1H, d, J = 17.0 Hz, CHCH_2), 2.96 (1H, dd, J = 17.0 and 10.5 Hz, CHCH_2), 1.48 (3H, d, J = 7.0 Hz, CHCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 170.0, 159.1, 158.5, 140.9, 136.9, 132.0, 128.5, 126.9, 114.9, 114.0, 111.4, 61.5, 55.5, 55.3, 52.4, 51.5, 29.3, 19.1; IR (film / cm^{-1}) ν = 1730 (C=O); HRMS: m/z (ES) 324.1601, $C_{20}H_{21}O_3N$ $[M+H]^+$ requires 324.1600; mp 128-130 °C; $[\propto]_D^{25}$ = -55 (*c* 0.60, $CHCl_3$).

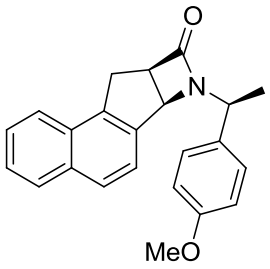
(2a*R*,7b*R*)-6,7-Dimethoxy-1-((*S*)-1-(4-methoxyphenyl)ethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one 280e



The title compound was prepared according to General Procedure **5** from (*S,E*)-ethyl 3-(3,4-dimethoxy-2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)propanoate **279e** (0.054 g, 0.14 mmol), which was dissolved in THF (5 mL) under a nitrogen atmosphere. 15-Crown-5 (0.03 mL, 0.15 mmol) and NaHMDS (1M in THF, 0.15 mL, 0.15 mmol) were added and the mixture was stirred for 8 hours at -40 °C and allowed to warm to room temperature. The crude product was purified using flash column chromatography [Petrol : EtOAc (60:40), R_f 0.15] yielding a white crystalline solid (0.029 g, 60 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.32-7.27 (2H, m, Ar), 6.95 (2H, d, J = 8.5 Hz, Ar), 6.77 (1H, s, C*H*COCH$_3$), 6.47 (1H, s, C*H*COCH$_3$), 4.95 (1H, q, J = 7.0 Hz, C*H*CH$_3$), 4.76 (1H, d, J = 4.0 Hz, CHC*H*N), 3.92-3.95 (1H, m, C*H*CH$_2$), 3.90 (3H, s, ArOC*H*$_3$), 3.87 (3H, s, ArOC*H*$_3$), 3.82 (3H, s, ArOC*H*$_3$), 3.34 (1H, d, J = 17.0 Hz, CHC*H*$_2$), 2.97 (1H, dd, J = 17.0 and 10.5 Hz, CHC*H*$_2$), 1.49 (3H, d, J = 7.0 Hz, CHC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 170.2, 159.1, 149.9, 147.9, 137.2, 132.1, 131.4, 128.5, 114.0, 108.8, 108.5, 61.9, 56.0, 55.9, 55.3, 52.4, 51.6, 30.0, 19.2; IR (film / cm^{-1}) ν = 1720 (C=O); HRMS: m/z (ES) 354.1692, $C_{21}H_{23}O_4N$ $[M+H]^+$ requires 354.1701; mp 142-144 °C; $[\alpha]_D^{25}$ = -3.5 (*c* 0.565, $CHCl_3$).

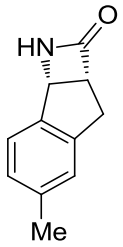
(2aR,7bR)-1-((S)-1-(4-methoxyphenyl)ethyl)-2,3-dihydro-1H-cyclopenta[a]-naphthalene[1,2-b]azet-2(7bH)-one 280f



The title compound was prepared according to General Procedure **5** from (*S,E*)-ethyl 3-(2-((1-(4-methoxyphenyl)ethylimino)methyl)naphthalen-1-yl)propanoate **279f** (0.068 g, 0.17 mmol), which was dissolved in dry THF (6 mL) under a nitrogen atmosphere. 15-crown-5 (0.04 mL, 0.19 mmol) and NaHMDS (1M in THF, 0.19 mL, 0.19 mmol) were added and the mixture was stirred for 8 hours at -40 °C and allowed to warm to room temperature. The crude product was purified using flash column chromatography [Petrol : EtOAc (60:40), R_f 0.39] yielding a white crystalline solid (0.034 g, 57 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.88 (1H, d, J = 8.0 Hz, Ar), 7.82 (1H, d, J = 8.0 Hz, Ar), 7.69 (1H, d, J = 8.0 Hz, Ar), 7.58-7.50 (2H, m, Ar), 7.32 (2H, d, J = 8.5 Hz, Ar), 7.23 (1H, d, J = 8.5 Hz, Ar), 6.95 (2H, d, J = 8.5 Hz, Ar), 5.02 (1H, q, J = 7.0 Hz, C*H*CH_3), 4.94 (1H, d, J = 4.0 Hz, NC*H*CH), 4.05 (1H, dq, J = 10.5 and 2.5 Hz, C*H*CH_2), 3.85 (3H, s, OCH_3), 3.75 (1H, d, J = 17.5 Hz, CHCH_2), 3.28 (1H, dd, J = 17.5 and 10.5 Hz, CHCH_2), 1.40 (3H, d, J = 7.0 Hz, CHCH_3); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$): δ_C = 170.0, 159.0, 141.8, 136.9, 133.5, 132.0, 131.0, 128.4, 127.4, 126.6, 126.3, 124.4, 123.4, 114.1, 62.3, 55.3, 51.8, 51.0, 28.7, 19.1; IR (film / cm^{-1}) ν = 1738 (C=O); HRMS: m/z (ES) 344.1648, $C_{23}H_{21}O_2N$ $[M+H]^+$ requires 344.1650; mp 149-151 °C; $[\propto]_D^{25}$ = +31 (*c* 0.49, $CHCl_3$).

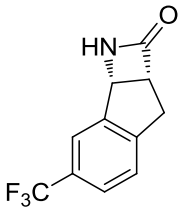
(2aR,7bR)-5-methyl-2a,3-Dihydro-1H-indeno[1,2-b]azet-2(7bH)-one 281a



(2a*R*,7b*R*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-5-methyl-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one (0.019 g, 0.06 mmol) **280a** was added to a solution of acetonitrile : water (5 mL : 1 mL). Ammonium cerium (IV) nitrate (0.10 g, 0.18 mmol) was added portion-wise and the solution was stirred for 16 hours. The reaction was quenched with a saturated solution of $NaHCO_3$ (30 mL) and diluted with diethyl ether (30 mL). The aqueous layer was extracted with diethyl ether (2 x 30 mL) and the organic layers combined and washed with a saturated solution of $NaHCO_3$ (2 x 30 mL). The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude was purified using flash column chromatography [Petrol : EtOAc (65:45), R_f 0.17] yielding a white crystalline solid (0.007 g, 66 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.23 (1H, d, J = 7.5 Hz, CH_3CCHCH), 7.12 (1H, s, CH_3CCHC), 7.06 (1H, d, J = 7.5 Hz, CH_3CCHCH), 6.19 (1H, br. s, N*H*), 5.01 (1H, d, J = 4.0 Hz, C*H*NH), 4.04 (1H, d, J = 10.5 Hz, C*H*CH_2), 3.33 (1H, dd, J = 17.5 Hz, CHCH_2), 3.05 (1H, dd, J = 17.5 and 10.5 Hz, CHCH_2), 2.37 (3H, s, CH_3); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ_C = 171.5, 144.5, 139.1, 137.7, 128.0, 126.9, 124.8, 58.3, 54.5, 30.3, 21.4; IR (film / cm^{-1}) ν = 3194 (N-H), 1701 (C=O); HRMS: m/z (ES) 174.0903, $C_{11}H_{11}ON$ $[M+H]^+$ requires 174.0910; mp 97-100 °C; $[\propto]_D^{21}$ = -140 (*c* 0.22, $CHCl_3$).

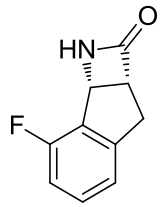
(2aR,7bR)-6-(Trifluoromethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one 281b



(2a*R*,7b*R*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-6-(trifluoromethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one (0.024 g, 0.07 mmol) **280b** was added to a solution of acetonitrile : water (5 mL : 1 mL). Ammonium cerium (IV) nitrate (0.11 g, 0.20 mmol) was added portion-wise and the solution was stirred for 16 hours. The reaction was quenched with a saturated solution of $NaHCO_3$ (30 mL) and diluted with diethyl ether (30 mL). The aqueous layer was extracted with diethyl ether (2 x 30 mL) and the organic layers combined and washed with a saturated solution of $NaHCO_3$ (2 x 30 mL). The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude was purified using flash column chromatography [Petrol : EtOAc (70:30), R_f 0.15] yielding a white crystalline solid (0.009 g, 61 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.62 (1H, s, CF_3CHC), 7.59 (1H, d, J = 8.0 Hz, CF_3CHCH), 7.42 (1H, d, J = 18.0 Hz CF_3CHCH), 6.35 (1H, br. s, N*H*), 5.09 (1H, d, J = 4.5 Hz, NC*H*CH), 4.12 (1H, m, C*H*CH_2), 3.42 (1H, d, J = 18.0 Hz, CHCH_2), 3.14 (1H, dd, J = 17.5 and 10.5 Hz, CHCH_2); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ_C = 170.5, 148.4, 141.3, 129.9 (q, J = 33.0 Hz, CF_3C) 126.8, 126.2 (q, J = 4.0 Hz, CHC*C*H), 124.0 (q, J = 272.0 Hz, *C*F_3), 122.3 (q, J = 4.0 Hz, CCH*C*H), 58.0, 54.6, 30.4; IR (film / cm^{-1}) ν = 3201 (N-H), 1755 (C=O); HRMS: m/z (ES) 228.0639, $C_{11}H_8ONF_3$ $[M+H]^+$ requires 228.0636; mp 138-139 °C; $[\propto]_D^{21}$ = -221 (*c* 0.24, $CHCl_3$).

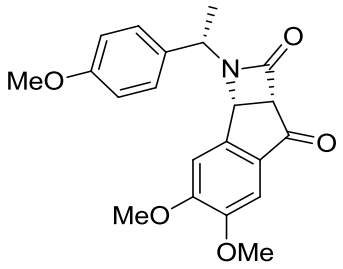
(2aR,7bR)-7-Fluoro-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one 281c



(2a*R*,7b*R*)-7-fluoro-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one (0.024 g, 0.08 mmol) **280c** was added to a solution of acetonitrile : water (5 mL : 1 mL). Ammonium cerium (IV) nitrate (0.13 g, 0.23 mmol) was added portion-wise and the solution was stirred for 16 hours. The reaction was quenched with a saturated solution of $NaHCO_3$ (30 mL) and diluted with diethyl ether (30 mL). The aqueous layer was extracted with diethyl ether (2 x 30 mL) and the organic layers combined and washed with a saturated solution of $NaHCO_3$ (2 x 30 mL). The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude was purified using flash column chromatography [Petrol : EtOAc (70:30), R_f 0.25] yielding a white crystalline solid (0.0085 g, 62 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.33-7.28 (1H, m, CFCHC*H*), 7.07 (1H, d, J = 7.5 Hz, CFCHCHC*H*), 6.92 (1H, app. t, J = 9.0 Hz, CFC*H*), 6.30 (1H, br. s, N*H*), 5.18 (1H, d, J = 4.5 Hz, NC*H*CH), 4.14-4.10 (1H, m, C*H*CH_2), 3.40 (1H, d, J = 17.5 Hz, CHC*H*$_2$), 3.10 (1H, dd, J = 17.5 and 10.5 Hz, CHC*H*$_2$); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ_C = 170.7, 160.1 (d, J = 248.0 Hz, *C*F), 147.8 (d, J = 4.5 Hz, CFC*C*CH), 131.4 (d, J = 7.0 Hz, CFCH*C*H), 127.6 (d, J = 19.0 Hz, CF*C*CCH), 121.9 (d, J = 19.0 Hz, CFCC*C*H), 113.5 (d, J = 19.0 Hz, CF*C*H), 55.2, 55.1, 30.6; IR (film / cm^{-1}) ν = 3225 (N-H), 1786 (C=O); HRMS: m/z (ES) 200.0472, $C_{10}H_8ONF$ $[M+Na]^+$ requires 200.0488; mp 151-153 °C; $[\propto]_D^{21}$ = -182 (*c* 0.28, $CHCl_3$).

(2aS,7bR)-5,6-Dimethoxy-1-((S)-1-(4-methoxyphenyl)ethyl)-1H-indeno[1,2-b]azete-2,3(2aH,7bH)-dione 282

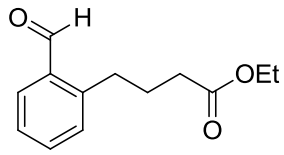


(2a*R*,7b*R*)-6,7-Dimethoxy-1-((*S*)-1-(4-methoxyphenyl)ethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one **280d** (0.020 g, 0.06 mmol) was added to a solution of acetonitrile : water (5 mL : 1 mL). Ammonium cerium (IV) nitrate (0.093 g, 0.17 mmol) was added portion-wise and the solution was stirred for 16 hours. The reaction was quenched with a saturated solution of $NaHCO_3$ (30 mL) and diluted with diethyl ether (30 mL). The aqueous layer was extracted with diethyl ether (2 x 30 mL) and the organic layers combined and washed with a saturated solution of $NaHCO_3$ (2 x 30 mL) The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure yielding a yellow oil (0.004 g, 19%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.18-7.12 (3H, m, Ar), 6.86-6.80 (2H, d, J = 8.5 Hz, Ar), 6.25 (1H, s, Ar), 4.82 (1H, q, J = 7.0 Hz, CH_3CH), 4.65 (1H, d, J = 3.5 Hz, COC*H*), 4.15 (1H, d, J = 3.5 Hz, NHC*H*CH), 3.84 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 1.44 (3H, d, J = 7.0 Hz, CH_3CH); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C = 193.6, 161.7, 159.4, 155.0, 150.9, 144.3, 131.4, 131.3, 128.6, 114.2, 108.2, 105.4, 63.1, 56.3, 56.2, 55.4, 53.5, 53.3, 19.4; IR (film / cm^{-1}) ν = 1729 (C=O); HRMS: m/z (ES) 370.1651, $C_{21}H_{23}O_5N$ $[M+H]^+$ requires 370.1654.

4.7 Synthesis and Optimization of Benzocishexacin

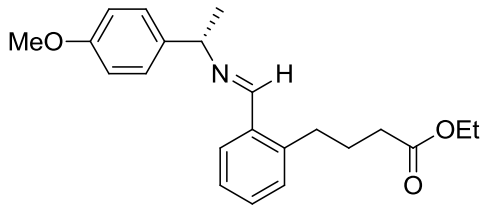
Ethyl 4-(2-formylphenyl)butanoate 291[169]



To a Schlenk flask flushed with nitrogen, anhydrous LiCl (0.75 g, 17.6 mmol) was added and dried under vacuum. Zinc dust (1.15 g, 17.6 mmol) was added and the resultant mixture was further dried under high vacuum. THF (10 mL) was added and the suspension was stirred for 10 minutes before dibromoethane (0.076 mL, 0.58 mmol), Me_3SiCl (0.015 mL, 0.12 mmol), iodine (0.09 g, 0.35 mmol) and ethyl 4-bromobutyrate (1.68 mL, 11.8 mmol) were added and the solution was stirred for 12 hours at 50 °C. The resultant grey suspension was cooled to room temperature and 2-bromobenzaldehyde (1.10 mL, 9.4 mmol), PEPPSI (0.04 g, 0.06 mmol) and DMI (5 mL) were added to the solution, which was stirred at room temperature for 12 hours. The reaction was quenched with a saturated solution of NH_4Cl (20 mL) and then filtered through cotton wool. The aqueous layer was extracted with diethyl ether (2 x 10 mL). The combined organics were collected, washed with brine (2 x 10 mL) and dried over $MgSO_4$. The solution was then filtered and the solvent evaporated under reduced pressure. The crude compound was purified using flash column chromatography [Petrol : EtOAc (90:10), R_f 0.50] yielding a yellow oil (0.90 g, 51 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.19 (1H, s, C*H*O), 7.77 (1H, app. dd, J = 7.5 and 1.5 Hz, Ar), 7.45 (1H, td, J = 7.5 and 1.5 Hz, Ar), 7.32 (1H, td, J = 7.5 and 1.5 Hz, Ar), 7.28-7.20 (1H, m, Ar), 4.06 (2H, q, J = 7.0 Hz, OC*H*$_2$CH$_3$), 3.01 (2H, t, J = 7.5 Hz, ArC*H*$_2$CH$_2$), 2.31 (2H, t, J = 7.5 Hz, CH$_2$CH$_2$C*H*$_2$), 1.93-1.82 (2H, pent., J = 7.5 Hz, ArCH$_2$C*H*$_2$), 1.19 (3H, t, J = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 192.5, 173.3, 144.3, 133.8, 133.7, 132.5, 131.2, 126.8, 60.4, 33.8, 31.8, 27.0, 14.3; IR (film / cm^{-1}) ν = 1728 (C=O), 1695 (C=O), 1600 (C-O); HRMS: m/z (ES) 243.0984, $C_{13}H_{16}O_3$ [M+Na]$^+$ requires 243.0997.

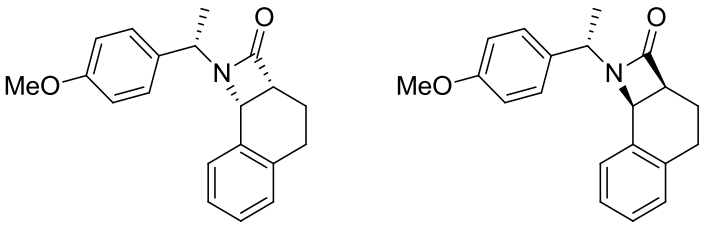
(*S*,*E*)-Ethyl 4-(2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)butanoate 285



Ethyl 4-(2-formylphenyl)butanoate (0.84 g, 3.8 mmol) **291** was dissolved in dry CH_2Cl_2 (50 mL) with $MgSO_4$ and stirred under a nitrogen atmosphere. After 5 minutes, (*S*)-(-)-4-methoxy-α-methylbenzylamine (0.56 mL, 3.8 mmol) was added and stirring was continued for 5 hours. The solution was then filtered and the solvent evaporated under reduced pressure yielding a colourless oil (1.10 g, 82 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.57 (1H, s, ArC*H*N), 7.82 (1H, app. dd, J = 7.5 and 1.5 Hz, C*H*CCHN), 7.28 (2H, d, J = 8.5 Hz, Ar), 7.24-7.13 (2H, m, Ar), 7.09 (1H, d, J = 7.0 Hz, $CH_3OCCHCH$), 6.81 (2H, d, J = 8.5 Hz, CH_3OCCH), 4.44 (1H, q, J = 6.5 Hz, C*H*CH_3), 4.06 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.71 (3H, s, OCH_3), 2.82 (2H, t, J = 7.5 Hz, ArCH_2CH_2), 2.25 (2H, t, J = 7.5 Hz, Ar$CH_2CH_2CH_2$), 1.82 (2H, p, J = 7.5 Hz, ArCH_2CH_2), 1.50 (3H, d, J = 6.5 Hz, CHCH_3), 1.18 (3H, t, J = 7.0 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 173.4, 158.5, 157.8, 141.2, 137.5, 134.1, 130.2, 130.1, 128.6, 127.7, 126.5, 113.8, 69.7, 60.3, 55.3, 33.8, 32.2, 26.9, 25.0, 14.3; HRMS: m/z (ES) 354.2074, $C_{22}H_{27}O_3N$ $[M+H]^+$ requires 354.2069.

(2a*R*,8b*R*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-1,3,4,8b-tetrahydronaphtho[1,2-b]-azet-2(2aH)-one 292



Major Minor

The title compound was prepared according to General Procedure **5** from (*S,E*)-ethyl 4-(2-((1-(4-methoxyphenyl)ethylimino)methyl)phenyl)butanoate **285** (0.064 g, 0.18 mmol), which was dissolved in THF (6 mL) under a nitrogen atmosphere. 15-Crown-5 (0.07

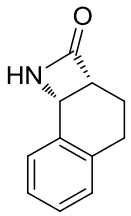
mL, 0.36 mmol) and NaHMDS (1 M in THF, 0.36 mL, 0.36 mmol) were added and the mixture was strirred for 8 hours at -40 °C and allowed to warm to room temperature. The crude was purified using flash column chromatography [Petrol : EtOAc (60:40), R_f 0.36] yielding a colourless oil (0.032 g, 57 %).

Major Diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.31-7.25 (1H, m, Ar), 7.22-7.17 (4H, m, Ar), 6.97-6.89 (3H, m, Ar), 4.99 (1H, q, J = 7.0 Hz, C*H*CH_3), 4.42 (1H, d, J = 5.0 Hz, NC*H*CH), 3.87 (3H, s, OC*H*$_3$), 3.59-3.55 (1H, m, NCHC*H*), 2.85-2.70 (2H, m, ArC*H*$_2$), 2.40 (1H, app. d of hep., J = 13.5 and 1.5 Hz, CHC*H*$_2$$CH_2$), 1.61-1.50 (1H, m, CHC*H*$_2$$CH_2$), 1.18 (3H, d, J = 7.0 Hz, CHC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 169.1, 158.9, 139.9, 133.7, 131.6, 130.1, 128.8, 128.7, 128.3, 126.2, 113.8, 55.3, 52.8, 50.6, 49.4, 26.8, 23.1, 18.2.

Minor Diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.31-7.25 (1H, m, Ar), 7.22-7.17 (2H, m, Ar), 7.10-7.07 (2H, m, Ar), 7.03 (1H, d, J = 7.5 Hz, Ar), 6.82-6.78 (2H, m, Ar), 4.50 (1H, d, J = 5.0 Hz, NC*H*CH), 4.32 (1H, q, J = 7.0 Hz, C*H*CH_3), 3.82 (3H, s, OC*H*$_3$), 3.59-3.55 (1H, m, NCHC*H*), 2.85-2.70 (2H, m, ArC*H*$_2$), 2.40 (1H, app. d of hep., J = 13.5 and 1.5 Hz, CHC*H*$_2$$CH_2$), 1.67 (3H, d, J = 7.0 Hz, CHC*H*$_3$), 1.47-1.40 (1H, m, CHC*H*$_2$$CH_2$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 169.4, 158.7, 139.9, 132.7, 131.6, 130.3, 128.8, 128.6, 128.3, 127.8, 114.0, 55.3, 52.8, 50.6, 49.2, 26.8, 22.9, 19.9.

IR (film / cm^{-1}) ν = 1727 (C=O); HRMS: m/z (ES) 308.1644, $C_{20}H_{21}O_2N$ $[M+H]^+$ requires 308.1650.

(2a*R*,8b*R*)-1,3,4,8b-Tetrahydronaphtho[1,2-b]azet-2(2aH)-one 293



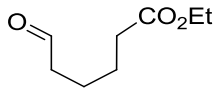
(2a*R*,8b*R*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-1,3,4,8b-tetrahydronaphtho[1,2-b]azet-2(2aH)-one **292** (0.027 g, 0.09 mmol) was added to a solution of acetonitrile : water (5 mL : 1 mL). Ammonium cerium (IV) nitrate (0.15 g, 0.27 mmol) was added portion-wise and the solution was stirred for 16 hours. The reaction was quenched with a saturated solution of $NaHCO_3$ (30 mL) and diluted with diethyl ether (30 mL). The aqueous layer

was extracted with diethyl ether (2 x 30 mL) and the organic layers combined and washed with a saturated solution of $NaHCO_3$ (2 x 30 mL). The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude product was purified using flash column chromatography [Petrol : EtOAc (70:30), R_f 0.29] yielding a white crystalline solid (0.011 g, 72 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.32-7.20 (4H, m, Ar), 6.06 (1H, br. s, N*H*), 4.70 (1H, d, J = 5.0 Hz, NC*H*CH), 3.74 (1H, s, C*H*CH_2CH_2), 2.88-2.73 (2H, m, $CHCH_2CH_2$), 2.35 (1H, d, J = 13.5 Hz, $CHCH_2CH_2$), 1.68-1.59 (1H, m, $CHCH_2CH_2$); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C = 170.6, 139.3, 134.0, 129.6, 129.0, 128.5, 126.6, 51.5, 50.2, 26.9, 22.9; IR (film / cm^{-1}) ν = 3235 (N-H), 1737 (C=O); HRMS: m/z (ES) 196.0721, $C_{11}H_{11}ON$ $[M+Na]^+$ requires 196.0738; mp 103-105 °C.

4.8 Chiral Imino Ester Synthesis

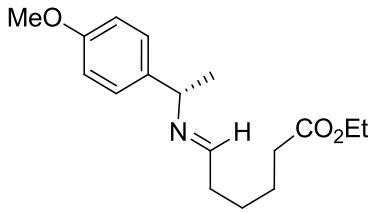
Ethyl 6-oxohexanoate 333



Ethyl-6-hydrohexanoate (0.50 mL, 3.1 mmol) was added to pyridinium chlorochromate (1.00 g, 3.1 mmol) in CH_2Cl_2 (14 mL) and allowed to stir at room temperature for 2 hours. The reaction mixture was filtered through a pad of Celite® and Fluorosil® and then evaporated under reduced pressure. The crude product was purified using flash column chromatography [Petrol : EtOAc (80:20), R_f 0.51] yielding a colourless liquid (0.44 g, 89 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 9.76 (1H, br. s, C*H*O), 4.13 (2H, q, J = 7.0 Hz, OCH_2CH_3), 2.46 (2H, app. q, CH_2CHO), 2.32 (2H, m, CH_2CO_2Et), 1.67 (4H, m, $CH_2CH_2CH_2$), 1.25 (3H, t, J = 7.0 Hz, OCH_2CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C = 201.9, 173.1, 60.1, 43.3, 33.8, 24.3, 21.4, 14.1; IR (film / cm^{-1}) ν = 1721 (C=O); HRMS: m/z (ES) 159.1013, $C_8H_{14}O_3$ $[M+H]^+$ requires 159.1021.

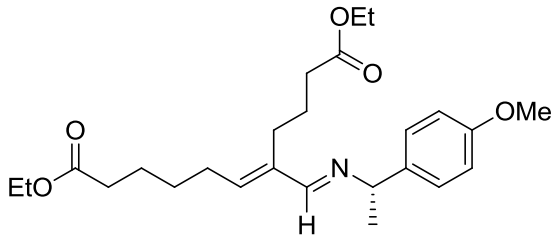
(*S*,*E*)-Ethyl 6-((1-(4-methoxyphenyl)ethyl)imino)hexanoate 334



Ethyl-6-oxohexanoate **333** (0.193 g, 1.22 mmol) was dissolved in dry CH_2Cl_2 (20 mL) with $MgSO_4$. After 5 minutes, (S)-(−)-4-Methoxy-α-methylbenzylamine (0.180 mL, 1.22 mmol) was added and the reaction was stirred for 3 hours. The solution was then filtered and the solvent evaporated under reduced pressure yielding a pale yellow oil (0.318 g, 90 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.71 (1H, t, J = 5.0 Hz, C*H*N), 7.29-7.20 (2H, m, Ar), 6.85 (2H, d, J = 8.5 Hz, Ar), 4.24 (1H, q, J = 6.5 Hz, CH_3CH), 4.11 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.78 (3H, s, OCH_3), 2.34-2.22 (4H, m, $CH_2CH_2CH_2CH_2$), 1.71-1.52 (4H, m, $CH_2CH_2CH_2$), 1.46 (3H, d, J = 6.5 Hz, CH_3CH), 1.24 (3H, t, J = 7.0 Hz, CH_2CH_3); HRMS: m/z (ES) 292.1911, $C_{17}H_{25}O_3N$ $[M+H]^+$ requires 292.1913.

(*E*)-Diethyl 5-((*E*)-(((*S*)-1-(4-methoxyphenyl)ethyl)imino)methyl)undec-5-enedioate 335

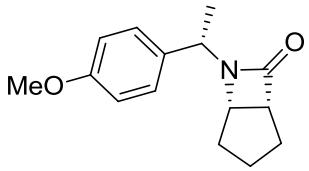


(*S*,*E*)-Ethyl 6-((1-(4-methoxyphenyl)ethyl)imino)hexanoate **334** was stored under nitrogen for 14 days, resulting in the formation of the title compound as a dark brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.82 (1H, s, C*H*N), 7.31 (2H, m, Ar), 6.90 (2H, m, Ar), 5.84 (1H, t, J = 7.5 Hz, CH_2CHCHN), 4.33 (1H, q, J = 6.5 Hz, $CHCH_3$), 4.16 (2H, q, J = 7.0 Hz, OCH_2CH_3), 4.15 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.82 (3H, s, OCH_3), 2.49 (2H, m, CCH_2), 2.35 (4H, m, O_2CCH_2), 2.28 (2H, m, CH_2CH), 1.81 (2H, m, CCH_2CH_2), 1.70

(2H, m, C*H*$_2$CH$_2$CH$_2$CH), 1.51 (2H, m, CH$_2$C*H*$_2$CH$_2$CH), 1.49 (3H, d, J = 6.5 Hz, CHC*H*$_3$), 1.29 (3H, t, J = 7.0 Hz, OCH$_2$C*H*$_3$), 1.28 (3H, t, J = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 173.7, 173.4, 162.3, 158.2, 141.5, 139.9, 137.9, 127.4, 113.7, 68.5, 60.1, 60.0, 55.2, 34.1, 34.0, 28.7, 27.9, 25.2, 25.1, 24.6, 24.0, 14.2, 14.1; HRMS: m/z (ES) 432.2752, $C_{25}H_{37}O_5N$ $[M+H]^+$ requires 432.2744.

(1*R*,5*S*)-6-((*S*)-1-(4-Methoxyphenyl)ethyl)-6-azabicyclo[3.2.0]heptan-7-one 336

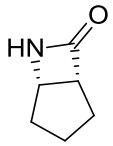


Ethyl 6-oxohexanoate **333** (0.28 g, 1.75 mmol) was dissolved in dry THF (35 mL) with $MgSO_4$ and left stirring under a nitrogen atmosphere. After 5 minutes, (*S*)-(−)-4-Methoxy-α-methylbenzylamine (0.26 mL, 1.75 mmol) was added to the reaction and stirred for 10 minutes, the solution was subsequently cooled to -40 °C. 15-Crown-5 (0.69 mL, 3.5 mmol) and NaHMDS (1M in THF, 3.5 mL, 3.5 mmol) were added and the mixture was stirred for 6 hours allowing to warm to room temperature. The reaction was quenched with a saturated solution of NH_4Cl (5 mL) and the THF was removed under reduced pressure. The resulting solution was further diluted with a saturated solution of NH_4Cl (20 mL) and the aqueous layer was extracted with Et_2O (3 x 30 mL). The organic layers were combined and washed with water (50 mL). The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude product was purified using flash column chromatography [Petrol : EtOAc (60:40), R_f 0.41] yielding a pale yellow oil (0.23 g, 52 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.26 (2H, m, Ar), 6.88 (2H, d, J = 8.5 Hz, Ar), 4.81 (1H, q, J = 7.0 Hz, CH$_3$C*H*), 3.83 (4H, m, OC*H*$_3$ and C*H*NH), 3.32 (1H, dd, J = 3.5 and 8.0 Hz, C*H*CHNH), 2.07-1.99 (1H, m, C*H*$_2$CH$_2$), 1.87-1.62 (3H, m, C*H*$_2$CH$_2$C*H*$_2$), 1.58 (3H, d, J = 7.0 Hz, C*H*$_3$CH), 1.38-1.13 (2H, m, CH$_2$C*H*$_2$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 168.9, 159.0, 132.9, 128.2, 114.0, 57.2, 55.3, 53.8, 51.5, 29.2, 24.8, 22.7, 19.6; IR (film / cm^{-1}) ν = 1731 (C=O); HRMS: m/z (ES) 246.1489, $C_{15}H_{19}O_2N$ $[M+H]^+$ requires 246.1494. $[\propto]_D^{21}$ = -14 (*c* 1.09, $CHCl_3$).

4.9 Synthesis of Cispentacin and Transpentacin Ethyl Ester

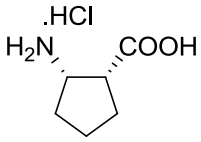
(1*R*,5*S*)-6-Azabicyclo[3.2.0]heptan-7-one 338



(1*R*,5*S*)-6-((*S*)-1-(4-Methoxyphenyl)ethyl)-6-azabicyclo[3.2.0]heptan-7-one **336** (0.297 g, 1.2 mmol) was added to a solution of acetonitrile : water (15 mL : 15 mL). Ammonium cerium (IV) nitrate (2.63 g, 4.8 mmol) was added portion-wise and the solution was stirred for 4 hours. The reaction was quenched with a saturated solution of $NaHCO_3$ (30 mL) and diluted with CH_2Cl_2 (30 mL). The aqueous layer was extracted with EtOAc (2 x 30 mL) and the organic layers combined and washed with a saturated solution of $NaHCO_3$ (2 x 30 mL) The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude product was purified by recrystallisation from dichloromethane and hexane yielding a white solid (0.095 g, 71 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 6.17 (1H, br. s, N*H*), 4.01 (1H, t, J = 4.0Hz, CHC*H*NH), 3.47-3.43 (1H, m, C*H*CHNH), 1.99 (1H, dd, J = 13.5 and 6.0 Hz, CH_2CH$_2$CH$_2$), 1.85-1.69 (3H, m, CH_2CH$_2$CH_2), 1.44-1.28 (2H, m, CH$_2$CH_2CH$_2$); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ_C = 171.0, 55.9, 54.0, 30.0, 25.2, 22.4; IR (film / cm^{-1}) ν = 3250 (N-H), 1716 (C=O); HRMS: m/z (ES) 112.0778, C_6H_9ON $[M+H]^+$ requires 112.0762; mp 49-50 °C; $[\propto]_D^{17}$ = -33 (*c* 0.87, $CHCl_3$).

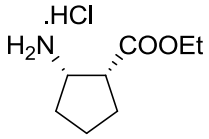
(1*R*,2*S*)-2-Aminocyclopentanecarboxylic acid hydrochloride 300a



(1*R*,5*S*)-6-Azabicyclo[3.2.0]heptan-7-one **338** (0.028 g, 0.25 mmol) was heated at reflux in 18% HCl solution for 3 hours. The solvent was then evaporated under reduced pressure. The crude product was purified by recrystallisation from water and diethyl ether yielding a white crystalline solid (0.040 g, 97 %).

^{1}H NMR (500 MHz, D_2O): δ_H = 3.84 (1H, q, J = 6.0 Hz, CHC*H*NH_2), 3.14 (1H, q, J = 8.5 Hz, C*H*CHNH_2), 2.17-2.09 (2H, m, CH_2CH_2CH_2), 1.98-1.69 (4H, m, CH_2CH_2CH_2). ^{13}C{^{1}H} NMR (125 MHz, D_2O): δ_C = 176.3, 52.7, 45.4, 29.7, 27.2, 21.2; IR (film / cm^{-1}) ν = 3341 (O-H), 2974 (N-H), 1694 (C=O); HRMS: m/z (ES) 152.0710, $C_6H_{11}O_2N$ [M+Na]$^+$ requires 152.0687; mp 164-166 °C; $[\propto]_D^{19}$ = -5.0 (*c* 0.5, H_2O).

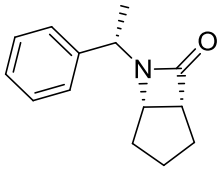
(1*R*,2*S*)-Ethyl 2-aminocyclopentanecarboxylate hydrochloride 338



(1*R*,5*S*)-6-Azabicyclo[3.2.0]heptan-7-one **339** (0.031 g, 0.28 mmol) was heated at reflux in ethanol (9 ml) with dry hydrogen chloride (1 M in Et_2O, 3 mL) for 3 hours. The solvent was then evaporated under reduced pressure. The crude product was purified by recrystallisation from diethyl ether yielding a white solid (0.052 g, 96 %);

^{1}H NMR (500 MHz, MeOD): δ_H = 4.27-4.16 (2H, m, OC$H_2$$CH_3$), 3.77 (1H, m, CHC*H*$NH_2$), 3.10 (1H, q, J = 8.0 Hz, C*H*CHNH_2), 2.19-2.08 (2H, m, CH_2CH_2CH_2), 2.03-1.73 (4H, m, CH_2CH_2CH_2), 1.28 (3H, t, J = 7.0 Hz, OCH_2CH_3). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C = 172.9, 61.0, 52.7, 45.4, 29.9, 27.3, 21.3, 13.0; IR (film / cm^{-1}) ν = 2957 (N-H), 1716 (C=O); HRMS: m/z (ES) 180.0998, $C_8H_{15}O_2N$ [M+Na]$^+$ requires 180.1000; $[\propto]_D^{19}$ = -7.77 (*c* 1.03, EtOH); mp 68-70 °C.

(1*R*,5*S*)-6-((*S*)-1-Phenylethyl)-6-azabicyclo[3.2.0]heptan-7-one 343

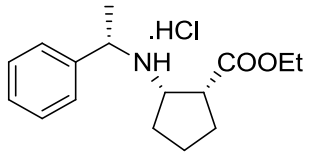


Ethyl 6-oxohexanoate **333** (0.69 g, 4.3 mmol) was dissolved in dry THF (80 mL) with $MgSO_4$ and stirred under a nitrogen atmosphere. After 5 minutes, (*S*)-α-methylbenzylamine (0.55 mL, 4.3 mmol) was added to the reaction and stirred for 10 minutes, the solution was subsequently cooled to -40 °C. 15-Crown-5 (1.72 mL, 8.6 mmol) and NaHMDS (1M in THF, 8.6 mL, 8.6 mmol) were added and the mixture was stirred for 8 hours allowing to warm to room temperature. The reaction was quenched

with a saturated solution of NH_4Cl (5 mL) and the THF was removed under reduced pressure. The resulting solution was further diluted with a saturated solution of NH_4Cl (20 mL) and the aqueous layer was extracted with Et_2O (3 x 30 mL). The organic layers were combined and washed with water (50 mL). The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude product was purified using flash column chromatography [Petrol : EtOAc (60:40), R_f 0.56] yielding a pale yellow oil (0.50 g, 53 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.29-7.17 (5H, m, Ar), 4.76 (1H, q, J = 7.0Hz, C*H*CH_3), 3.76 (1H, t, J = 4.0 Hz, C*H*NH), 3.26 (1H, dd, J = 8.0 and 3.5 Hz, C*H*CHNH), 1.96 (1H, dd, J = 13.0 and 6.0 Hz, C*H*$_2$$CH_2CH_2$), 1.80-1.56 (3H, m, C*H*$_2$$CH_2$C*H*$_2$), 1.54 (3H, d, J = 7.0 Hz, CHC*H*$_3$), 1.33-1.04 (2H, m, CH_2C*H*$_2$$CH_2$); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C = 168.9, 140.8, 128.6, 127.6, 127.0, 57.33, 53.9, 52.1, 29.2, 24.8, 22.7, 19.5; IR (film / cm^{-1}) ν = 1726 (C=O); HRMS: m/z (ES) 238.1309, $C_{14}H_{17}ON$ $[M+Na]^+$ requires 238.1208; = -11.0 (*c* 0.64, $CHCl_3$).

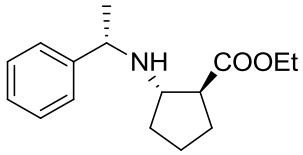
(1*R*,2*S*)-Ethyl 2-(((*S*)-1-phenylethyl)amino)cyclopentanecarboxylate 344



(1*R*,5*S*)-6-((*S*)-1-Phenylethyl)-6-azabicyclo[3.2.0]heptan-7-one **343** (0.13 g, 0.60 mmol) was heated at reflux in ethanol (18 ml) with dry hydrogen chloride (1 M in Et_2O , 6 mL) for 12 hours. The solvent was then evaporated under reduced pressure yielding the title compound as a brown oil (0.17 g, 95 %).

^{1}H NMR (300 MHz, MeOD): δ_H = 7.58-7.53 (3H, m, Ar), 7.51-7.42 (2H, m, Ar), 4.45 (1H, q, J = 7.0 Hz, C*H*CH_3), 4.29-4.17 (2H, m, OCH_2C*H*$_3$), 3.42 (1H, q, J = 7.5 Hz, C*H*NH), 3.18 (1H, m, C*H*CHNH), 2.07-1.72 (5H, m, C*H*$_2$$CH_2$C*H*$_2$), 1.69 (3H, d, J = 7.0 Hz, CHC*H*$_3$), 1.64-1.54 (1H, m, CH_2C*H*$_2$$CH_2$), 1.29 (3H, t, J = 7.0 Hz, OCH_2C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, MeOD): δ_C = 175.3, 137.9, 131.3, 131.0, 129.4, 63.1, 60.4, 59.7, 45.6, 29.6, 22.6, 20.5, 14.8; IR (film / cm^{-1}) ν = 3391 (N-H), 1725 (C=O); HRMS: m/z (ES) 284.1604, $C_{16}H_{23}O_2N$ $[M+Na]^+$ requires 284.1626; $[\propto]_D^{19}$ = -47.4 (*c* 1.31, MeOH).

(1*S*,2*S*)-Ethyl 2-(((*S*)-1-phenylethyl)amino)cyclopentanecarboxylate 345

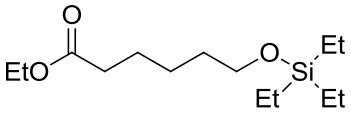


(1*R*,2*S*)-Ethyl 2-(((*S*)-1-phenylethyl)amino)cyclopentanecarboxylate **344** (0.16 g, 0.55 mmol) was dissolved in dry ethanol (8 mL) under a nitrogen atmosphere. Potassium *tert*-butoxide (0.12g, 1.10 mmol) was added and the reaction was heated at reflux for 4 hours. After cooling, the reaction was quenched with NH_4Cl (5 mL) and the aqueous layer extracted with dichloromethane (2 x 30 mL). The combined organics were collected and washed with water (2 x 30 mL) and then dried over $MgSO_4$. The solvent was then evaporated under reduced pressure. The crude product was purified using flash column chromatography [Petrol : EtOAc (90:10), R_f 0.15] yielding a colourless oil (0.79 g, 55 %) in accordance with the literature.[213]

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.33-7.30 (4H, m, Ar), 7.26-7.21 (1H, m, Ar), 4.16-4.08 (2H, m, OC*H*$_2$CH$_3$), 3.86 (1H, q, J = 7.0 Hz, C*H*CH$_3$), 3.23 (1H, q, J = 7.0 Hz, C*H*NH), 2.60 (1H, q, J = 7.0 Hz, C*H*CHNH), 2.01-1.92 (1H, m, C*H*$_2$CHNH), 1.81 (2H, hep., J = 7.5 Hz, CH$_2$C*H*$_2$C*H*$_2$), 1.72- 1.57 (2H, m, C*H*$_2$CH$_2$CH$_2$), 1.36 (3H, d, J = 6.5 Hz, CHC*H*$_3$), 1.33-1.27 (1H, m, CH$_2$C*H*$_2$CH$_2$), 1.24 (3H, t, J = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 176.0, 128.3, 126.9, 126.7, 61.6, 60.3, 56.8, 51.3, 34.3, 28.9, 24.6, 23.7, 14.1; IR (film / cm^{-1}) ν = 1727 (C=O); HRMS: m/z (ES) 262.1562, $C_{16}H_{23}O_2N$ $[M+H]^+$ requires 262.1807; $[\alpha]_D^{21}$ = -1.4 (*c* 0.71, $CHCl_3$).

4.10 α–Methyl-Substituted Cispentacin Synthesis

Ethyl 6-((triethylsilyl)oxy)hexanoate 350

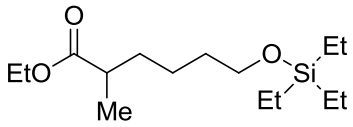


A solution of ethyl 6-hydroxyhexanoate **332** (1.5 mL, 9.2 mmol) in CH_2Cl_2 (90 mL) was cooled to 0 °C under a nitrogen atmosphere. 2,6-Lutidine (2.1 mL, 18.4 mmol) was added followed by a dropwise addition of TES-triflate (3.1 mL, 13.7 mmol), the resulting solution was then stirred for 3 hours at 0 °C. Following this, the reaction was quenched

with water (30 mL) and extracted with Et_2O (3 x 30 mL), the organic layers were combined and further washed with water (30 mL). The organics were dried using $MgSO_4$ and filtered; the solvent was then removed under reduced pressure. The crude product was purified using flash column chromatography [Petrol : EtOAc (95:5), R_f 0.71] yielding a colourless oil (1.95 g, 77 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 4.09 (2H, q, J = 7.0 Hz, OC*H*$_2$CH$_3$), 3.57 (2H, t, J = 6.5 Hz, C*H*$_2$OSi), 2.27 (2H, t, J = 7.5 Hz, EtOOCC*H*$_2$), 1.67-1.56 (2H, pent., J = 7.5 Hz, $CH_2CH_2CH_2O$), 1.54-1.46 (2H, q, J = 7.0 Hz, C*H*$_2$CH$_2$CH$_2$O), 1.40-1.28 (2H, m, CH$_2$C*H*$_2$CH$_2$O), 1.22 (3H, t, J = 7.0 Hz, OCH$_2$C*H*$_3$), 0.92 (9H, t, J = 8.0 Hz, SiCH$_2$C*H*$_3$), 0.56 (6H, q, J = 8.0 Hz, SiC*H*$_2$CH$_3$); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C = 173.7, 62.6, 60.1, 34.3, 32.5, 25.4, 24.8, 14.2, 6.7, 4.6; IR (film / cm^{-1}) ν = 1737 (C=O) 1095 (Si-O); HRMS: m/z (ES) 297.1724, $C_{14}H_{30}O_3Si$ [M+Na]$^+$ requires 297.1862.

Ethyl 2-methyl-6-((triethylsilyl)oxy)hexanoate 351

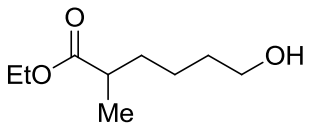


A solution of NaHMDS (1M in THF, 1.5 mL, 1.5 mmol) in THF (15 mL) was cooled to -78 °C, followed by a dropwise addition of ethyl 6-((triethylsilyl)oxy)hexanoate **350** (0.35 g, 1.2 mmol). The reaction was left for 4 hours and allowed to warm to -40 °C, methyl iodide (0.13 mL, 2.04 mmol) was subsequently added and the resulting solution was left overnight to warm to room temperature. The reaction was quenched with a saturated solution of NH_4Cl (20 mL) and the aqueous layer was extracted with Et_2O (3 x 30 mL). The organic layers were combined and washed with brine (30 mL). The organics were then dried using $MgSO_4$ and filtered before the solvent was removed under reduced pressure. The crude product was purified using flash column chromatography [Petrol : EtOAc (95:5), R_f 0.74] yielding a yellow oil (0.24 g, 65 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 4.12 (2H, q, J = 7.0 Hz, OC*H*$_2$CH$_3$), 3.59 (2H, t, J = 6.5 Hz, C*H*$_2$OSi), 2.41 (1H, sextet, J = 7.0 Hz, C*H*CH$_3$), 1.73-1.28 (6H, m, C*H*$_2$C*H*$_2$C*H*$_2$), 1.24 (3H, t, J = 7.0 Hz, OCH$_2$C*H*$_3$), 1.13 (3H, d, J = 7.0 Hz, C*H*$_3$CH) 0.95 (9H, t, J = 8.0 Hz, SiCH$_2$C*H*$_3$), 0.58 (6H, q, J = 8.0 Hz, SiC*H*$_2$CH$_3$). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C

= 176.9, 62.7, 60.1, 39.6, 33.6, 32.8, 23.6, 17.0, 14.3, 6.8, 4.4; IR (film / cm^{-1}) ν = 1736 (C=O) 1096 (Si-O); HRMS: m/z (ES) 289.2186, $C_{15}H_{32}O_3Si$ $[M+H]^+$ requires 289.2199.

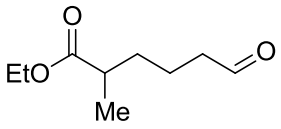
Ethyl 6-hydroxy-2-methylhexanoate 352



TBAF (1M in THF, 1.85 mL, 1.85 mmol) was slowly added to a solution of ethyl 2-methyl-6-((triethylsilyl)oxy)hexanoate **351** (0.27 mL, 0.92 mmol) in THF (15 mL) and left for 30 minutes. The reaction was quenched with a saturated solution of NH_4Cl (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The organics were then dried using $MgSO_4$ and filtered before the solvent was removed under reduced pressure. The crude product was purified using flash column chromatography [Petrol : EtOAc (95:5), R_f 0.10] yielding a yellow oil (0.11 g, 67 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 4.12 (2H, q, J = 7.0 Hz, OC$H_2$$CH_3$), 3.64 (2H, t, J = 6.5 Hz, CH_2OH), 2.48-2.36 (1H, sextet, J = 7.0 Hz, C$H$$CH_3$), 1.76-1.30 (6H, m, J = 7.0 Hz, CH_2CH_2CH_2), 1.25 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.15 (3H, d, J = 7.0 Hz, C$H$$CH_3$); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C = 176.8, 62.7, 60.2, 39.5, 33.4, 32.6, 23.4, 17.1, 14.3; IR (film / cm^{-1}) ν = 3404 (O-H), 1733 (C=O); HRMS: m/z (ES) 175.1347, $C_9H_{18}O_3$ $[M+H]^+$ requires 175.1334.

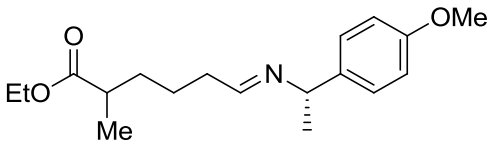
Ethyl 2-methyl-6-oxohexanoate 353



Ethyl 6-hydroxy-2-methylhexanoate **352** (0.062 mL, 0.35 mmol) was added to pyridinium chlorochromate (0.11 g, 0.51 mmol) in CH_2Cl_2 (5 mL) and allowed to stir at room temperature for 3 hours. The reaction mixture was filtered through a pad of Celite® and Fluorosil® and the solvent evaporated under reduced pressure. The crude product was purified using flash column chromatography [Petrol : EtOAc (80:20), R_f 0.80] yielding a colourless oil (0.037 g, 60 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 9.76 (1H, t, J = 1.5 Hz, C*H*O), 4.13 (2H, q, J = 7.0 Hz, OC*H*$_2$), 2.48-2.38 (3H, m, C*H*CH_3 and C*H*$_2$CHO), 1.69-1.27 (4H, m, C*H*$_2$C*H*$_2$$CH_2$), 1.22 (3H, m, OCH_2C*H*$_3$), 1.16 (3H, d, J = 7.0 Hz, CHC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 201.2, 175.5, 59.4, 42.8, 38.5, 32.2, 18.9, 16.2, 13.4; IR (film / cm^{-1}) ν = 1726 (C=O); HRMS: m/z (ES) 173.1191, $C_9H_{16}O_3$ $[M+H]^+$ requires 173.1178.

(*E*)-Ethyl 6-(((S)-1-(4-methoxyphenyl)ethyl)imino)-2-methylhexanoate 354

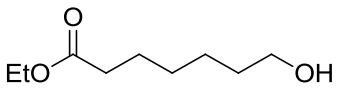


Ethyl 2-methyl-6-oxohexanoate **353** (0.038 g, 0.22 mmol) was dissolved in dry CH_2Cl_2 (6 mL) with $MgSO_4$. After 5 minutes (*S*)-(−)-4-Methoxy-α-methylbenzylamine (0.032 mL, 0.22 mmol) was added and the reaction was stirred for 3 hours. The solution was then filtered and the solvent evaporated under reduced pressure yielding a pale yellow oil (0.061 g, 91 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.71 (1H, t, J = 4.5 Hz, CH*N*), 7.29-7.20 (2H, m, Ar), 6.90-6.83 (2H, m, Ar), 4.23 (1H, q, J = 6.5 Hz, ArC*H*CH_3), 4.11 (2H, q, J = 7.0 Hz, OC*H*$_2$$CH_3$), 3.78 (3H, s, OC*H*$_3$), 2.48-2.22 (2H, m, C*H*$_2$CHN), 1.73-1.49 (4H, m, C*H*C*H*$_3$), 1.48-1.43 (3H, d, ArCHC*H*$_3$), 1.43-1.10 (7H, m, C*H*$_2$C*H*$_2$ and OCH_2C*H*$_3$).

4.11 Synthesis of Cishexacin

Ethyl 7-hydroxyheptanoate 357

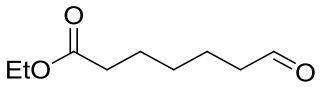


Potassium persulfate (5.00 g, 18.50 mmol) was added to a solution of H_2SO_4 (4.60 mL), ethanol (10 mL) and water (2 mL), which had been cooled to 15 °C. A solution of cycloheptanone **356** (0.73 g, 6.17 mmol) in ethanol (3 mL) was added dropwise and the reaction was left to stir overnight. The reaction was diluted with water (30 mL) and the aqueous layer was extracted with Et_2O (3 x 30 mL). The organics were collected, dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude

product was purified by distillation ($bp_{0.2}$ = 114-116 °C) yielding a colourless oil (0.838 g, 74 %) in accordance with the literature.[203]

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 4.02 (2H, q, J = 7.0 Hz, OC*H*$_2$CH$_3$), 3.52 (2H, t, J = 6.5 Hz, C*H*$_2$OH), 2.38 (1H, br. s, O*H*), 2.20 (2H, t, J = 7.5 Hz, EtOOCC*H*$_2$), 1.60-1.40 (4H, m, C*H*$_2$CH$_2$CH$_2$C*H*$_2$), 1.33-1.21 (4H, m, CH$_2$C*H*$_2$C*H*$_2$CH$_2$), 1.51 (3H, t, J = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 173.9, 62.6, 60.2, 34.2, 32.4, 28.6, 25.4, 24.8, 14.2; IR (film / cm^{-1}) ν = 3389 (O-H), 1732 (C=O); HRMS: m/z (ES) 175.1323, $C_9H_{18}O_3$ $[M+H]^+$ requires 175.1334.

Ethyl 7-oxoheptanoate 358

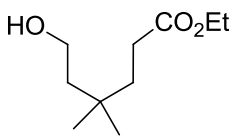


Ethyl 7-hydroxyheptanoate **357** (0.737 mL, 4.23 mmol) was added to pyridinium chlorochromate (1.37 g, 6.34 mmol) in CH_2Cl_2 (20 mL) and allowed to stir at room temperature for 2 hours. The reaction mixture was filtered through a pad of Celite® and Fluorosil® and then evaporated under reduced pressure. The crude product was purified by distillation ($bp_{0.2}$ = 96-98°C) yielding a colourless oil (0.714 g, 98 %) in accordance with the literature.[203]

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 9.69 (1H, s, C*H*O), 4.05 (2H, q, J = 7.0 Hz, OC*H*$_2$CH$_3$), 2.38 (2H, t, J = 7.0 Hz, C*H*$_2$CHO), 2.23 (2H, t, J = 7.0 Hz, EtOCOC*H*$_2$), 1.66-1.49 (4H, m, CH$_2$C*H*$_2$C*H*$_2$), 1.37-1.23 (2H, m, C*H*$_2$CH$_2$CH$_2$), 1.18 (3H, t, J = 6.5 Hz, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C = 202.5, 173.5, 60.2, 43.6, 34.1, 28.5, 24.7, 21.6, 14.2; IR (film / cm^{-1}) ν = 1725 (C=O).

4.12 Gem-Di-Methyl Substituted Cispentacin Synthesis

Ethyl 6-hydroxy-4,4-dimethylhexanoate 369

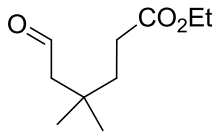


Potassium persulfate (2.40 g, 8.87 mmol) was added to a solution of H_2SO_4 (5 mL), ethanol (10 mL) and water (2 mL), which has been cooled to 15 °C. A solution of 4,4'-

dimethylcyclohexanone **364** (0.373 g, 2.96 mmol) in ethanol (3 mL) was added dropwise and the reaction was left to stir overnight. The reaction was diluted with water (30 mL) and the aqueous layer was extracted with Et_2O (3 x 30 mL). The organics were collected, dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude product was purified using flash column chromatography [Petrol : EtOAc (80:20), R_f- 0.23] yielding a colourless oil (0.445 g, 80 %).[203]

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 4.05 (2H, q, J = 7.0 Hz, OC*H*$_2$), 3.61 (2H, t, J = 7.0 Hz, C*H*$_2$OH), 2.68 (1H, br. s, O*H*), 2.25-2.17 (2H, m, C*H*$_2$CO$_2$Et), 1.54-1.40 (4H, m, C*H*$_2$C(CH$_3$)$_2$C*H*$_2$), 1.19 (3H, t, J = 7.0 Hz, OCH$_2$C*H*$_3$), 0.83 (6H, s, C (C*H*$_3$)$_2$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 174.4, 60.4, 59.5, 44.0, 36.9, 31.9, 29.6, 27.1, 14.2; IR (film / cm^{-1}) ν = 3413 (O-H), 1733 (C=O); HRMS: m/z (ES) 189.1486, $C_{10}H_{20}O_3$ $[M+H]^+$ requires 189.1490.

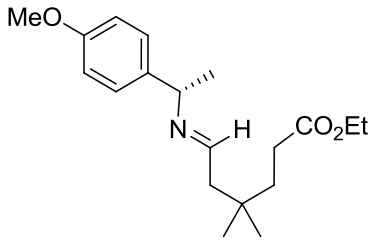
Ethyl 4,4-dimethyl-6-oxohexanoate 370



Pyridinium chlorochromate (0.589 g, 2.73 mmol) was added to ethyl 6-hydroxy-4,4-dimethylhexanoate **369** (0.343 mL, 1.82 mmol) in CH_2Cl_2 (15 mL) and allowed to stir at room temperature for 2 hours. The reaction mixture was filtered through a pad of Celite® and Fluorosil® and then evaporated under reduced pressure. The crude product was purified using flash column chromatography [Petrol : EtOAc (80:20), R_f - 0.79] yielding a colourless oil (0.295 g, 87 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 9.80 (1H, s, C*H*O), 4.15-4.01 (2H, br. s, OC*H*$_2$CH$_3$), 2.34-2.18 (4H, br. s, C*H*$_2$CHO and C*H*$_2$CO$_2$), 1.75-1.59 (2H, br. s, C*H*$_2$C(CH$_3$)$_2$), 1.30-1.15 (3H, br. s, OCH$_2$C*H*$_3$), 1.10-0.95 (6H, s, C(C*H*$_3$)$_2$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 202.9, 173.6, 60.5, 54.5, 37.1, 33.1, 29.4, 27.0, 14.2; IR (film / cm^{-1}) ν = 1732 (C=O); HRMS: m/z (ES) 187.1340, $C_{10}H_{18}O_3$ $[M+H]^+$ requires 187.1334.

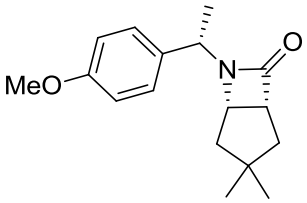
(*S*,*E*)-Ethyl 6-((1-(4-methoxyphenyl)ethyl)imino)-4,4-dimethylhexanoate 371



Ethyl 4,4-dimethyl-6-oxohexanoate **370** (0.183 g, 0.98 mmol) was dissolved in dry CH_2Cl_2 (20 mL) with $MgSO_4$. After 5 minutes (*S*)-(−)-4-Methoxy-α-methylbenzylamine (0.145 mL, 0.98 mmol) was added and the reaction was stirred for 3 hours. The solution was then filtered and the solvent evaporated under reduced pressure yielding a pale yellow oil (0.272 g, 87 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.72 (1H, t, J = 5.5 Hz, CN*H*), 7.17 (2H, d, J = 8.5 Hz, Ar), 6.78 (2H, d, J = 8.5 Hz, Ar), 4.20 (1H, q, J = 6.5 Hz, C*H*CH_3), 4.04 (2H, q, J = 7.0 Hz, OC*H*$_2$$CH_3$), 3.71 (3H, s, OC*H*$_3$), 2.26-2.19 (2H, m, C*H*$_2$CO), 2.11 (2H, d, J = 5.5 Hz, C*H*$_2$C$(CH_3)_2$), 1.57-1.50 (2H, m, C*H*$_2$CHN), 1.41 (3H, d, J = 6.5 Hz, CHC*H*$_3$), 1.17 (3H, t, J = 7.0 Hz, OCH_2C*H*$_3$), 0.87 (6H, s, C(C*H*$_3$)$_2$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 174.0, 161.5, 158.4, 137.0, 127.6, 114.1, 113.8, 69.3, 60.3, 55.3, 47.0, 37.0, 33.3, 29.5, 27.0, 24.3, 14.2; IR (film / cm^{-1}) ν = 1731 (C=O), 1661 (C=N), 1611 (C-O).

(1*R*,5*S*)-6-((*S*)-1-(4-Methoxyphenyl)ethyl)-3,3-dimethyl-6-azabicyclo[3.2.0]heptan-7-one 372

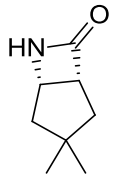


(*S*,*E*)-Ethyl 6-((1-(4-methoxyphenyl)ethyl)imino)-4,4-dimethylhexanoate **371** (0.378 g, 1.18 mmol) was dissolved in THF (40 mL). 15-Crown-5 (0.47 mL, 2.36 mmol) and NaHMDS (1 M in THF, 2.36 mL, 2.36 mmol) were added and the mixture was stirred for 8 hours at room temperature. The reaction was quenched with a saturated solution of NH_4Cl (5 mL) and the THF was removed under reduced pressure. The resulting solution was further diluted with a saturated solution of NH_4Cl (20 mL) and the aqueous

layer was extracted with Et_2O (3 x 30 mL). The organic layers were combined and washed with water (50 mL). The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude product was purified using flash column chromatography [Petrol : EtOAc (60:40), R_f 0.57] yielding a pale yellow oil (0.252 g, 78 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.19-7.14 (2H, m, Ar), 6.84-6.78 (2H, m, Ar), 4.85 (1H, q, J = 7.0 Hz, C*H*CH_3), 3.80-3.75 (1H, m, CHC*H*N), 3.74 (3H, s, OC*H*$_3$), 3.36 (1H, ddd, J = 9.0, 4.5 and 2.0 Hz, C*H*CHN), 1.81 (1H, dd, J = 14.0 and 2.0 Hz, C*H*$_2$C(CH_3)CH_2), 1.67 (1H, d, J = 14.5 Hz, CH_2C(CH_3)C*H*$_2$), 1.49 (3H, d, J = 7.0 Hz, CHC*H*$_3$), 1.39-1.27 (2H, m, C*H*$_2$C(CH_3)C*H*$_2$), 1.08 (3H, s, C(C*H*$_3$)$_2$), 0.94 (3H, s, C(C*H*$_3$)$_2$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 170.3, 158.9, 132.7, 128.3, 113.9, 57.9, 55.3, 55.2, 50.6, 43.2, 42.0, 38.3, 31.2, 30.1, 18.8; IR (film / cm^{-1}) ν = 1737 (C=O); HRMS: m/z (ES) 296.1644, $C_{17}H_{23}O_2N$ [M+Na]$^+$ requires 296.1626; $[\propto]_D^{21}$ = -18 (*c* 0.55, $CHCl_3$).

(1*R*,5*S*)-3,3-Dimethyl-6-azabicyclo[3.2.0]heptan-7-one 372

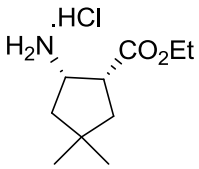


(1*R*,5*S*)-6-((*S*)-1-(4-Methoxyphenyl)ethyl)-3,3-dimethyl-6-azabicyclo[3.2.0]heptan-7-one **373** (0.227 g, 0.83 mmol) was added to a solution of acetonitrile : water (20 mL : 20 mL). Ammonium cerium (IV) nitrate (1.82 g, 3.32 mmol) was added portion-wise and the solution was stirred for 4 hours. The reaction was then quenched with a saturated solution of $NaHCO_3$ (30 mL) and diluted with CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL) and the organic layers combined and washed with a saturated solution of $NaHCO_3$ (2 x 30 mL) The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude product was purified by recrystallisation from Et_2O and petrol yielding a white crystalline solid (0.100 g, 87 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 5.99 (1H, br. s, N*H*), 4.17 (1H, t, J = 5.0 Hz, C*H*NH), 3.64-3.59 (1H, m, CHC*H*), 1.99 (1H, dd, J = 14.0 and 5.0 Hz, C*H*$_2$C(CH_3)CH_2), 1.76 (1H, d, J = 14.5 Hz, CH_2C(CH_3)C*H*$_2$), 1.61-1.53 (2H, m, C*H*$_2$C(CH_3)C*H*$_2$), 1.25 (3H, s,

C(C*H*$_3$)$_2$), 1.10 (3H, s, C(C*H*$_3$)$_2$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 172.3, 57.4, 55.9, 44.1, 41.9, 39.5, 31.5, 30.1; IR (film / cm^{-1}) ν = 3218 (N-H), 1735 (C=O); HRMS: m/z (ES) 140.1056, $C_8H_{13}ON$ $[M+H]^+$ requires 140.1075; mp 95-97 °C; $[\propto]_D^{17}$ = -2 (*c* 1.01, $CHCl_3$).

(1*R*,2*S*)-Ethyl 2-amino-4,4-dimethylcyclopentanecarboxylate hydrochloride 374

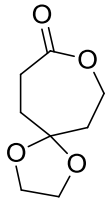


(1*R*,5*S*)-3,3-Dimethyl-6-azabicyclo[3.2.0]heptan-7-one **373** (0.017 g, 0.12 mmol) was heated at reflux in ethanol (4 ml) with dry hydrogen chloride (1 M in Et_2O, 2 mL) for 3 hours. The solvent was then evaporated under reduced pressure. The crude product was purified by recrystallisation from CH_2Cl_2 and hexane yielding a white crystalline solid (0.024 g, 90 %).

^{1}H NMR (500 MHz, MeOD): δ_H = 4.29-4.18 (2H, m, OC*H*$_2$CH$_3$), 3.89 (1H, q, J = 7.5 Hz, CHC*H*NH$_2$), 3.33 (1H, m, C*H*CHNH$_2$), 2.06 (1H, dd, J = 13.5 and 7.5 Hz, CHC*H*$_2$), 1.94 (2H, d, J = 8.5 Hz, C*H*$_2$CHCHC*H*$_2$), 1.71 (1H, dd, J = 13.5 and 8.0 Hz, NH$_2$CHCHC*H*$_2$), 1.31 (3H, t, J = 7.0 Hz, OCH$_2$C*H*$_3$), 1.18 (3H, s, C(C*H*$_3$)$_2$), 1.08 (3H, s, C(C*H*$_3$)$_2$); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C = 173.3, 61.7, 52.3, 44.8, 44.6, 43.3, 37.2, 29.9, 29.8, 14.2; IR (film / cm^{-1}) ν = 3417 (N-H) 1721 (C=O) 1208 (C-O); HRMS: m/z (ES) 208.1297, $C_{10}H_{19}O_2N$ $[M+Na]^+$ requires 208.1313; $[\propto]_D^{22}$ = -4.6 (*c* 0.86, MeOH).

4.13 Cyclisation of Acetal Substrate

1,4,8-Trioxaspiro[4.6]undecan-9-one 376

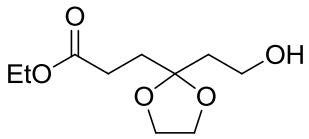


To a stirred solution of 1,4-cyclohexadione monoethylene acetal **375** (2.1 g, 13.3 mmol) in CH_2Cl_2 (20 mL), mCPBA (3.4 g, 19.9 mmol) was added and heated at reflux for 6 hours. The reaction was allowed to cool to room temperature, dried using $MgSO_4$ and

the solvent evaporated under reduced pressure.[214] The crude product was purified using flash column chromatography [Petrol : EtOAc (70:30), R_f 0.50] yielding a translucent white solid (1.8 g, 80 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 4.29 (2H, m, COOC*H*$_2$), 3.98 (4H, m, OC*H*$_2$C*H*$_2$*O*), 2.70 (2H, m, OCOC*H*$_2$), 2.00 (2H, m, OCOCH$_2$C*H*$_2$), 1.90 (2H, m, COOCH$_2$C*H*$_2$); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C = 175.4, 107.8, 64.8, 64.3, 39.0, 32.7, 28.8; IR (film / cm^{-1}) ν = 1725 (C=O); HRMS: m/z (ES) 173.0804, $C_8H_{13}O_4$ [M+H]$^+$ requires 173.0808; mp 48-50 °C.

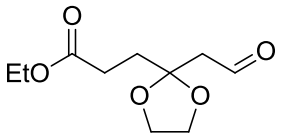
Ethyl 3-(2-(2-hydroxyethyl)-1,3-dioxolan-2-yl)propanoate 377



The lactone 1,4,8-trioxaspiro[4.6]undecan-9-one **376** (0.15 g, 0.87 mmol) was dissolved in ethanol (5 mL) and cooled to 0 °C. K_2CO_3 (0.024 g, 0.17 mmol) was added and the reaction was stirred for 1 hour at 0 °C. The reaction was then filtered and the filtrate was concentrated under reduced pressure.[207] The crude product was purified using flash column chromatography [Petrol : EtOAc (30:70), R_f 0.38] yielding a translucent white liquid (0.16 g, 87 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 4.11 (2H, q, J = 7.0 Hz, C*H*$_2$CH$_3$), 3.97 (4H, m, OC*H*$_2$C*H*$_2$O), 3.73 (2H, t, J = 5.5 Hz, C*H*$_2$OH), 2.70 (1H, br. s, O*H*), 2.35 (2H, m, O$_2$CC*H*$_2$), 2.02 (2H, t, J = 7.5 Hz, O$_2$CCH$_2$C*H*$_2$), 1.89 (2H, t, J = 5.5 Hz, C*H*$_2$CH$_2$OH), 1.24 (3H, t, J = 7.0 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C = 173.3, 111.2, 64.9, 60.4, 58.7, 38.4, 32.0, 28.9, 14.2; IR (film / cm^{-1}) ν = 3439 (O-H), 1732 (C=O); HRMS: m/z (ES) 241.1169, $C_{10}H_{18}O_5$ [M+Na]$^+$ requires 241.1154.

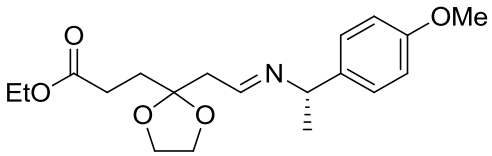
Ethyl 3-(2-(2-oxoethyl)-1,3-dioxolan-2-yl)propanoate 378



Ethyl 3-(2-(2-hydroxyethyl)-1,3-dioxolan-2-yl)propanoate **377** (0.81 mL, 3.71 mmol) was added to pyridinium chlorochromate (1.20 g, 5.57 mmol) in CH_2Cl_2 (20 mL) and allowed to stir at room temperature for 2 hours. The reaction mixture was filtered through a pad of Celite® and Fluorosil® and the solvent was evaporated under reduced pressure. The crude product was purified using flash column chromatography [Petrol : EtOAc (30:70), R_f 0.70] yielding a pale yellow liquid (0.72 g, 89 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 9.73 (1H, t, J = 3.0 Hz, C*H*O), 4.13 (2H, q, J = 7.0 Hz, OC*H*$_2$CH$_3$), 4.00 (4H, m, OC*H*$_2$C*H*$_2$O), 2.68 (2H, d, J = 3.0 Hz, C*H*$_2$CHO), 2.39 (2H, m, O$_2$CC*H*$_2$), 2.09 (2H, m, O$_2$CCH$_2$C*H*$_2$), 1.25 (3H, t, J = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C = 199.9, 173.0, 108.5, 65.3, 60.5, 50.7, 33.3, 28.6, 14.2; IR (film / cm^{-1}) ν = 1722 (C=O); HRMS: m/z (ES) 217.1070, $C_{10}H_{16}O_5$ $[M+H]^+$ requires 217.1076.

(*S*,*E*)-Ethyl-3-(2-(2-((1-(4-methoxyphenyl)ethyl)imino)ethyl)-1,3-dioxolan-2-yl)propanoate 379

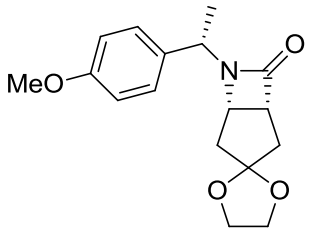


Ethyl 3-(2-(2-oxoethyl)-1,3-dioxolan-2-yl)propanoate **378** (0.421 g, 1.95 mmol) was dissolved in dry CH_2Cl_2 (20 mL) with $MgSO_4$. After 5 minutes (*S*)-(−)-4-Methoxy-α-methylbenzylamine (0.288 mL, 1.95 mmol) was added and the reaction was stirred for 3 hours. The solution was then filtered and the solvent evaporated under reduced pressure yielding a colourless oil (0.668 g, 98 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.74 (1H, td, J = 5.5 and 0.5 Hz, C*H*N), 7.30-7.23 (2H, m, Ar), 6.90-6.84 (2H, m, Ar), 4.29 (1H, q, J = 6.5 Hz, C*H*CH$_3$), 4.12 (2H, q, J = 7.0 Hz, OC*H*$_2$CH$_3$), 3.93 (4H, m, OC*H*$_2$C*H*$_2$O), 3.79 (3H, s, OC*H*$_3$), 2.61 (2H, d, J = 5.5 Hz, C*H*$_2$CHN), 2.38 (2H, m, O$_2$CC*H*$_2$), 2.02 (2H, m, O$_2$CCH$_2$C*H*$_2$), 1.49 (3H, d, J = 6.5 Hz,

CHC*H*$_3$), 1.25 (3H, t, J = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C{^{1}H}c NMR (100 MHz, $CDCl_3$): δ_C = 173.3, 159.1, 158.5, 136.8, 127.6, 113.8, 109.6, 69.2, 65.2, 60.3, 55.3, 43.9, 32.9, 28.6, 24.1, 14.2; IR (film / cm^{-1}) ν = 1732 (C=O), 1663 (C=N).

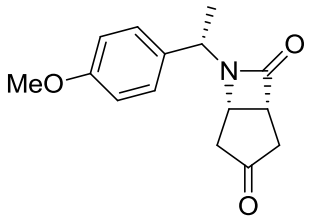
(1*R*,5*S*)-6-((*S*)-1-(4-Methoxyphenyl)ethyl)-6-azaspiro[bicyclo[3.2.0]heptane-3,2'-[1,3]dioxolan]-7-one 380



The title compound was prepared according to General Procedure **5** from (*S*,*E*)-Ethyl 3-(2-(2-((1-(4-methoxyphenyl)ethyl)imino)ethyl)-1,3-dioxolan-2-yl)propanoate **379** (0.12 g, 0.33 mmol), which was dissolved in dry THF (10 mL) under a nitrogen atmosphere. 15-crown-5 (0.13 mL, 0.67 mmol) and NaHMDS (1M in THF, 0.67 mL, 0.67 mmol) were added and the mixture was stirred for 8 hours at -40 °C and allowed to warm to room temperature. The crude product was purified using flash column chromatography [Petrol : EtOAc (40:60), R_f 0.13] yielding a white crystalline solid (0.060 g, 59 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.26 (2H, m, Ar), 6.89 (2H, m, Ar), 4.94 (1H, q, J = 7.0 Hz, C*H*CH$_3$) 4.03-3.78 (8H, m, COC*H*$_3$, OC*H*$_2$C*H*$_2$ *and* NC*H*), 3.44 (1H, ddd, J = 9.0, 4.5 and 1.0 Hz, NCHC*H*), 2.20 (1H, dt, J = 14.0 and 1.0 Hz, O$_2$CC*H*$_2$), 2.03 (1H, dd, J = 14.5 and 1.0 Hz, O$_2$CC*H*$_2$), 1.84-1.67 (2H, m, O$_2$CC*H*$_2$), 1.60 (3H, d, J = 7.0 Hz, CHC*H*$_3$); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C = 168.4, 158.9, 132.5, 128.4, 116.5, 113.9, 64.6, 64.3, 55.3, 53.5, 51.2, 50.9, 38.0, 34.6, 19.0; IR (film / cm^{-1}) ν = 1740 (C=O); HRMS: m/z (ES) 304.1543, $C_{17}H_{21}O_4N$ $[M+H]^+$ requires 304.1542; mp 49-51 °C; $[\propto]_D^{20}$ = -7.96 (*c* 1.01, $CHCl_3$).

(1*R*,5*S*)-6-((*S*)-1-(4-methoxyphenyl)ethyl)-6-azabicyclo[3.2.0]heptane-3,7-dione 382[209]

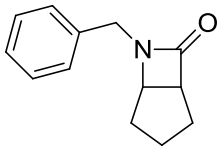


(1*R*,5*S*)-6-((*S*)-1-(4-Methoxyphenyl)ethyl)-6-azaspiro[bicyclo[3.2.0]heptane-3,2'-[1,3]-dioxolan]-7-one **380** (0.043 g, 0.14 mmol) and iodine (0.004 g, 0.014 mmol) was stirred in acetone (5 mL) at room temperature for 30 minutes. The acetone was evaporated under reduced pressure and the residue dissolved in CH_2Cl_2. The organic layer was separated, washed with $Na_2S_2O_3$ (10 mL) and brine (20 mL), dried with $MgSO_4$ and the solvent evaporated under reduced pressure. The crude product was purified using flash column chromatography [Petrol : EtOAc (20:80), R_f 0.33] yielding a colourless oil (0.029 g, 79 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.22 (2H, m, Ar), 6.88 (2H, m, Ar), 4.83 (1H, q, J = 8.5 Hz, C*H*CH_3) 4.05 (1H, m, NC*H*), 3.79 (3H, s, OCH_3), 3.66 (1H, ddd, J = 10.5, 5.0 and 2.0 Hz, NCHC*H*), 2.62 (1H, m, COCH_2), 2.46-2.23 (3H, m, CH_2COCH_2), 1.58 (3H, d, J = 7.5 Hz, CHCH_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C = 214.3, 167.9, 159.2, 131.9, 128.4, 114.2, 55.3, 52.0, 51.8, 49.1, 41.7, 37.0, 19.5; IR (film / cm^{-1}) ν = 1738 (C=O), 1671 (C=O); HRMS: m/z (ES) 282.1078, $C_{15}H_{17}O_3N$ $[M+H]^+$ requires 282.1106; $[\propto]_D^{20}$ = -30.6 (*c* 1.18, $CHCl_3$).

4.14 Future Work - Enantioselective Cyclisation

6-Benzyl-6-azabicyclo[3.2.0]heptan-7-one 388



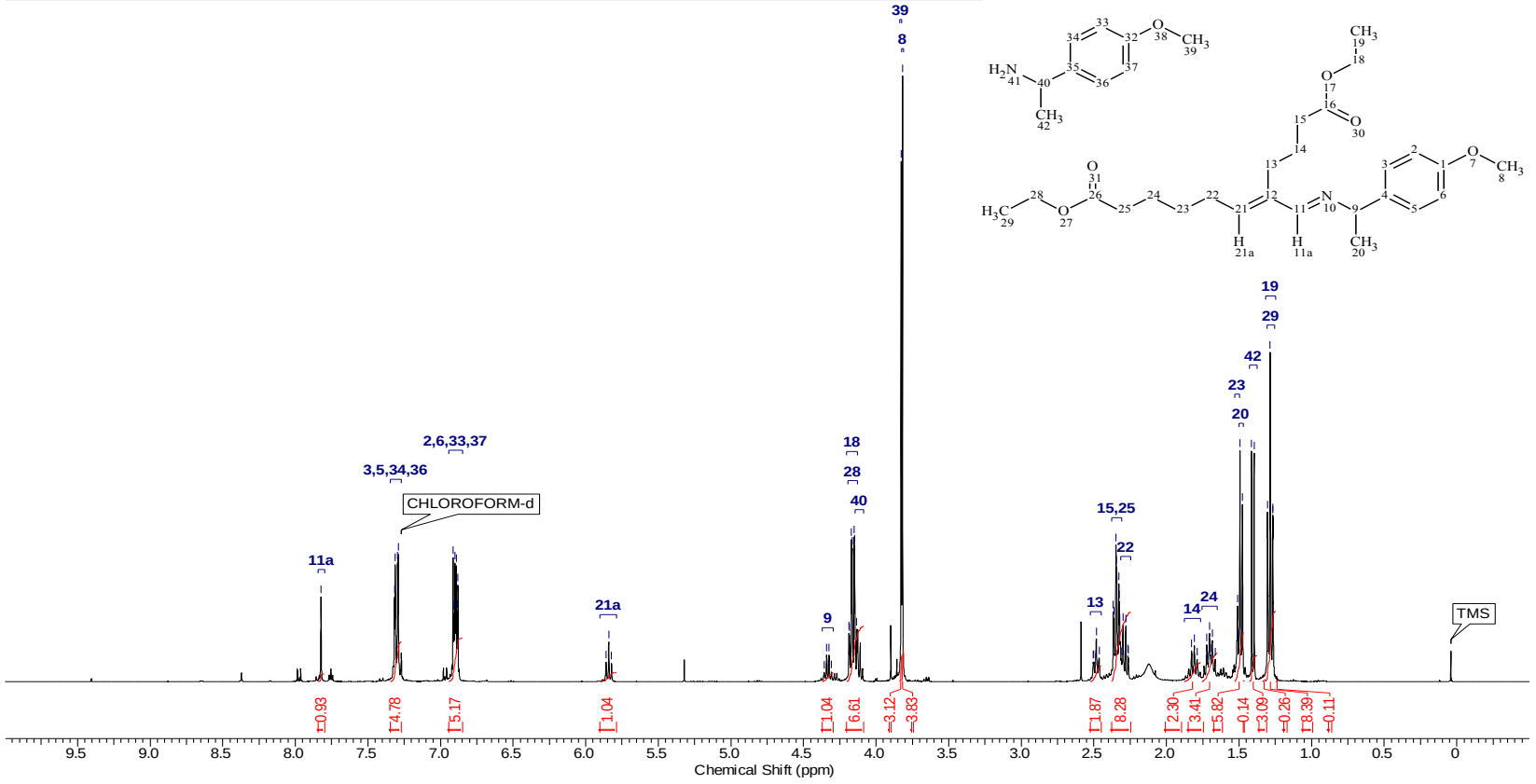
Ethyl 6-oxohexanoate **333** (0.95 g, 5.97 mmol) was dissolved in dry THF (100 mL) with $MgSO_4$ and left stirring under a nitrogen atmosphere. After 5 minutes benzylamine (0.65 mL, 5.97 mmol) was added to the reaction and stirred for 10 minutes, the solution was subsequently cooled to -40 °C. NaHMDS (1 M in THF, 12.0 mL, 12.0 mmol) was added and the mixture was stirred for 8 hours, allowing to warm to room temperature. The reaction was quenched with a saturated solution of NH_4Cl (5 mL) and the THF was removed under reduced pressure. The resulting solution was further diluted with a saturated solution of NH_4Cl (20 mL) and the aqueous layer was extracted with Et_2O (3 x 30 mL). The organic layers were combined and washed with water (50 mL). The organics were then dried using $MgSO_4$ and filtered before being evaporated under reduced pressure. The crude product was purified using flash column chromatography [Petrol : EtOAc (60:40), R_f 0.35] yielding a colourless oil (0.70 g, 58 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.37-7.24 (5H, m, Ar), 4.48 (1H, dd, J = 15.0 and 2.0 Hz, NCH_2), 4.09 (1H, dd, J = 15.0 and 1.0 Hz, NCH_2), 3.90 (1H, t, J = 5.0 Hz, NCH), 3.45 (1H, dd, J= 7.5 and 3.0 Hz, NCHCH), 2.03 (1H, m, CH_2CH_2CH_2), 1.75 (2H, m, CH_2CH_2CH_2), 1.57 (1H, m, CH_2CH_2CH_2), 1.38 (1H, m, CH_2CH_2CH_2), 1.18 (1H, m, CH_2CH_2CH_2); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C = 169.4, 136.2, 128.7, 128.2, 127.6, 57.5, 54.9, 44.0, 26.8, 24.9, 22.7; IR (film / cm^{-1}) ν = 1743 (C=O).

5 Appendix

5.1 ^{1}H NMR Spectrum of Dimer Impurity 335

Acquisition Time (sec)	4.6399	***Comment***	Caroline Evans/CE-5-054/ID			***Date***	01 Nov 2011 21:43:28
Date Stamp	01 Nov 2011 21:43:28						
File Name	\\UKMCDILSNEEZY.RD.ASTRAZENECA.NET\NMRDATA.:DATA\MCUS02PDD\NMR\111101032\11\PDATA\1\1R						
Frequency (MHz)	400.13	***Nucleus***	1H	***Number of Transients***	8	***Origin***	A400
Original Points Count	32768	***Owner***	ian	***Points Count***	65536	***Pulse Sequence***	sthq.z
Receiver Gain	256.00	***SW(cyclical) (Hz)***	7062.15	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2486.0417	***Sweep Width (Hz)***	7062.04	***Temperature (degree C)***	27.000		



5.2 ^{13}C NMR Spectrum of Dimer Impurity 335

Acquisition Time (sec)	1.3282	***Comment***	Caroline Evans/CE-5-054/ID			***Date***	01 Nov 2011 21:32:48
Date Stamp	01 Nov 2011 21:32:48						
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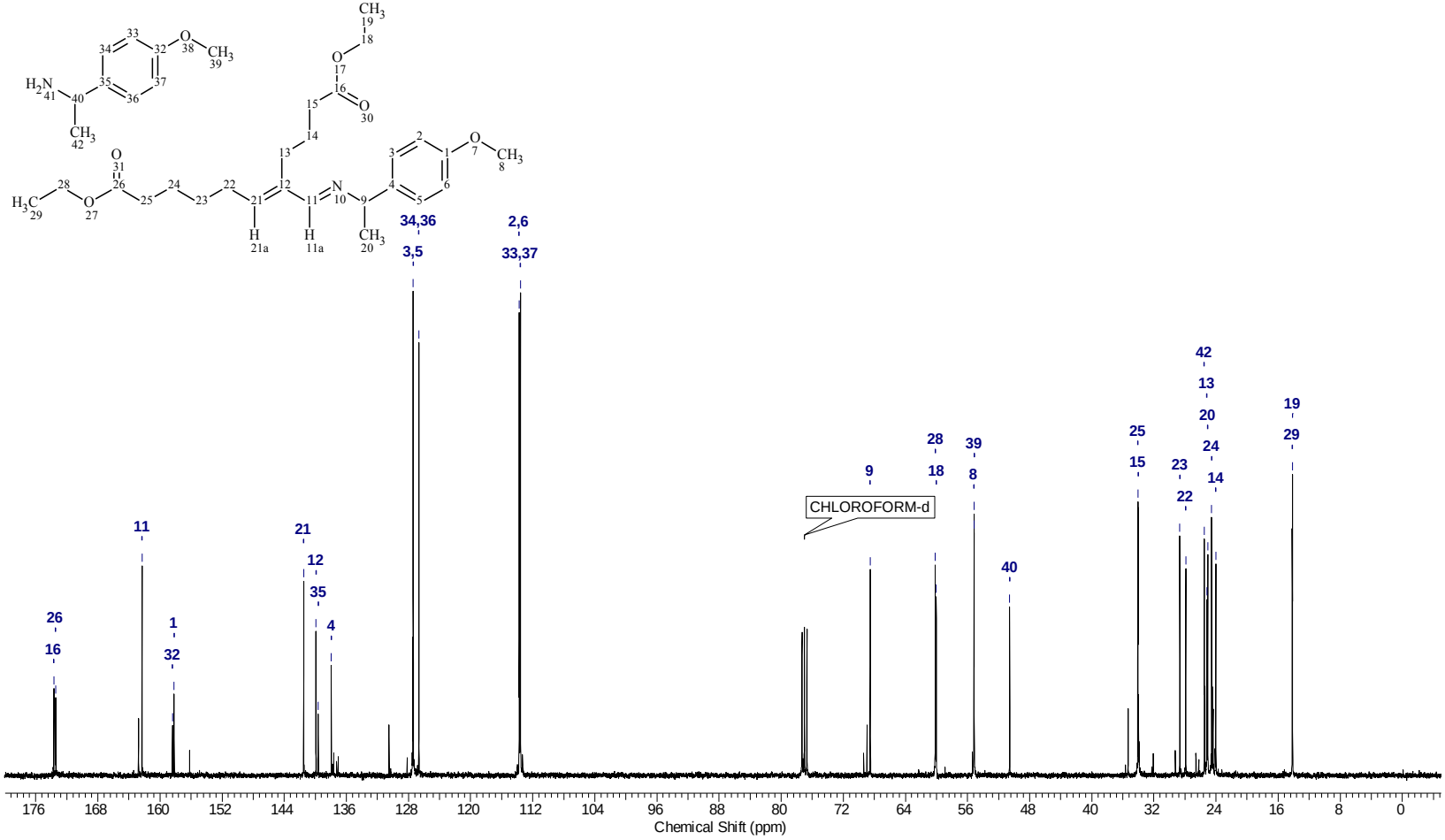
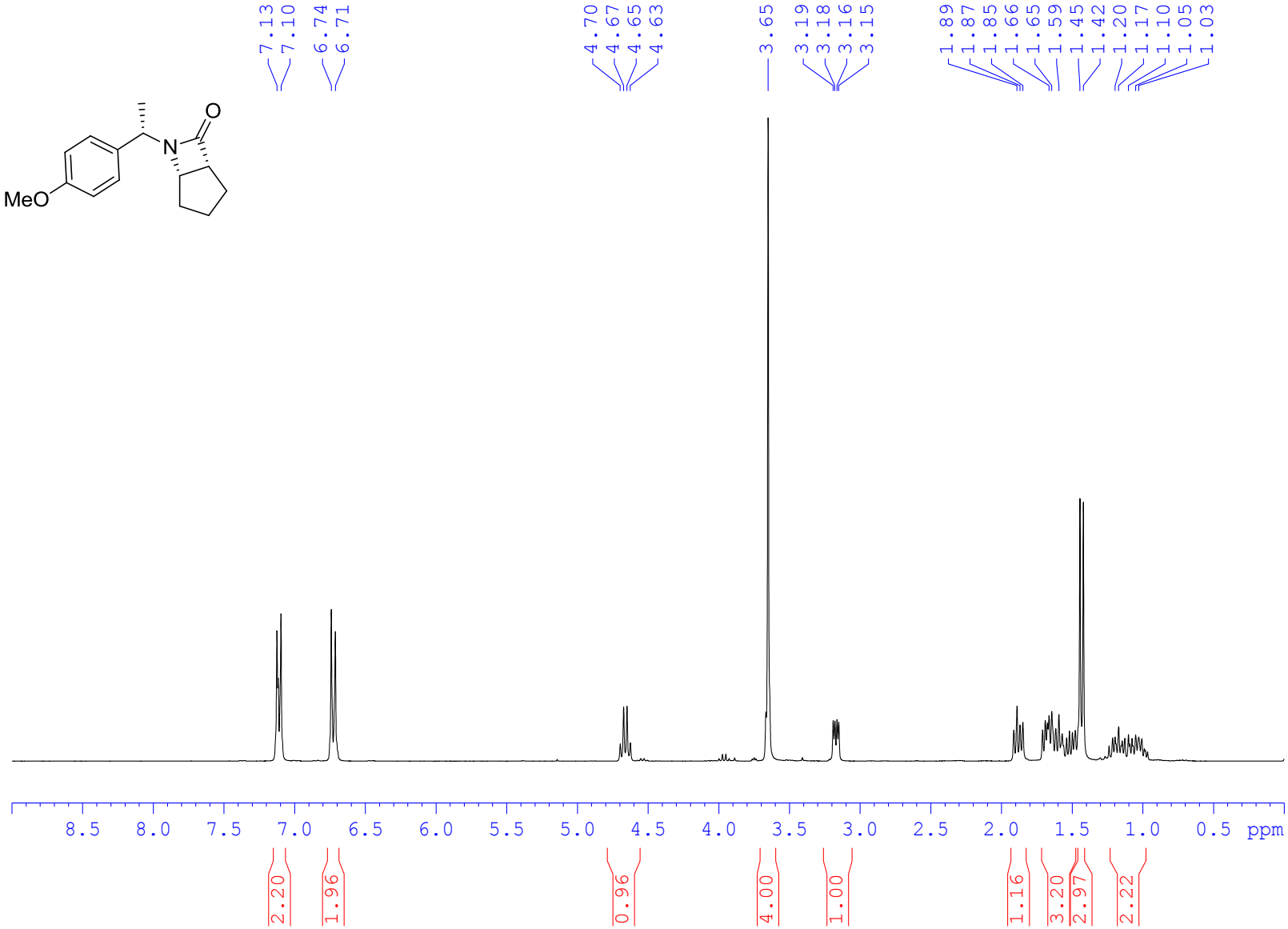
Frequency (MHz)	100.61	***Nucleus***	13C	***Number of Transients***	800	***Origin***	A400
Original Points Count	32768	***Owner***	ian	***Points Count***	65536	***Pulse Sequence***	stc.z
Receiver Gain	2050.00	***SW(cyclical) (Hz)***	24671.05	***Solvent***	CHLOROFORM-d	***Spectrum Offset (Hz)***	10054.2598
Sweep Width (Hz)	24670.68	***Temperature (degree C)***	27.000				



5.3 ^{1}H NMR Spectrum of β-lactam 336



5.4 X-ray Crystal Structure Data for Trifluoro-aryl-β-lactam 280b

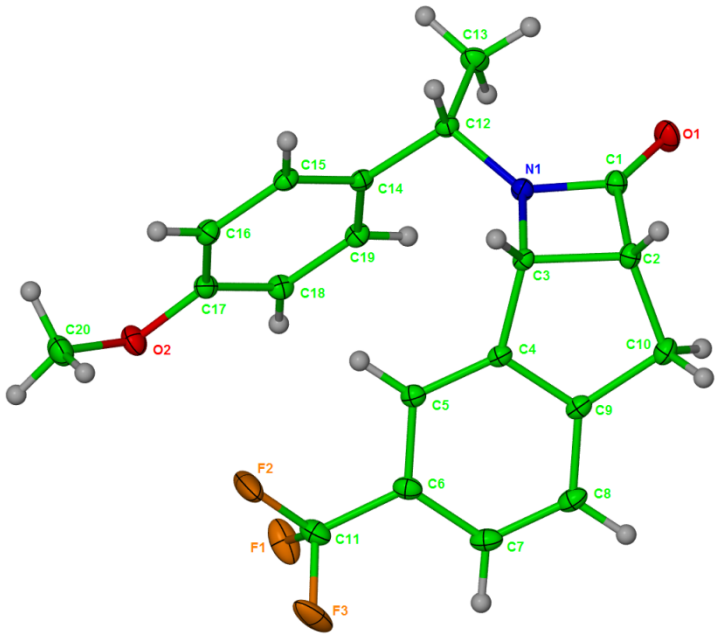


Figure 37- X-ray crystal structure of trifluoro-aryl-β-lactam 280b with ellipsoids drawn at the 50% probability level.

Table 18- Crystal data & structure refinement for (2a*R*,7b*R*)-1-((*S*)-1-(4-Methoxyphenyl)ethyl)-6-(trifluoromethyl)-2a,3-dihydro-1H-indeno[1,2-b]azet-2(7bH)-one 280b

Empirical formula	C20 H18 F3 N O2
Formula weight	361.35
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21
Unit cell dimensions	a = 7.1850(1)Å $\alpha = 90^o$
	b = 6.2670(1)Å $\beta = 99.040(1)^o$
	c = 18.5790(4)Å $\gamma = 90^o$
Volume	826.19(2) $Å^3$
Z	2
Density (calculated)	1.453 Mg/m^3
Absorption coefficient	0.116 mm^{-1}
F(000)	376
Crystal size	0.35 x 0.25 x 0.2 mm
Theta range for data collection	4.04 to 27.50^o
Index ranges	-9<=h<=9; -8<=k<=7; -24<=l<=24
Reflections collected	15805
Independent reflections	3741 [R(int) = 0.0331]
Reflections observed (>2σ)	3570
Data Completeness	0.990
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.966 and 0.920
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3741 / 31 / 265
Goodness-of-fit on F^2	1.052
Final R indices [I>2σ(I)]	R1 = 0.0295 wR2 = 0.0746
R indices (all data)	R1 = 0.0316 wR2 = 0.0763
Absolute structure parameter	-0.4(5)
Largest diff. peak and hole	0.157 and -0.148 $eÅ^{-3}$

Notes: 50:50 disorder of the fluorine positions was readily modeled with inclusion of of C-F and F…F distance restraints. Absolute stereochemistry not definitive from structural results; assignment made on the basis of know stereochemistry at C12.

Table 19- Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for trifluoro-aryl-β-lactam 280b U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
F(1)	6643(9)	11436(10)	9504(5)	57(1)
F(2)	5152(14)	8750(10)	9057(4)	72(2)
F(3)	3730(7)	11165(14)	9544(4)	61(2)
F(1A)	6745(9)	11188(14)	9411(5)	89(3)
F(2A)	4747(14)	8823(10)	9040(5)	80(2)
F(3A)	3968(10)	11528(16)	9590(4)	79(2)
O(1)	6543(1)	14035(2)	5199(1)	40(1)
O(2)	9978(1)	7311(2)	9081(1)	36(1)
N(1)	6360(1)	11395(2)	6097(1)	23(1)
C(1)	5766(2)	13022(2)	5624(1)	27(1)
C(2)	3784(2)	13037(2)	5831(1)	25(1)
C(3)	4505(2)	11169(2)	6349(1)	22(1)
C(4)	4385(2)	11992(2)	7099(1)	23(1)
C(5)	4846(2)	10938(2)	7763(1)	25(1)
C(6)	4544(2)	11985(2)	8395(1)	29(1)
C(7)	3814(2)	14051(2)	8369(1)	33(1)
C(8)	3361(2)	15096(2)	7705(1)	32(1)
C(9)	3648(2)	14054(2)	7068(1)	26(1)
C(10)	3198(2)	14871(2)	6294(1)	30(1)
C(11)	5008(2)	10863(2)	9111(1)	36(1)
C(12)	7819(2)	9742(2)	6121(1)	24(1)
C(13)	9449(2)	10526(2)	5757(1)	33(1)
C(14)	8435(2)	9031(2)	6902(1)	23(1)
C(15)	8029(2)	7003(2)	7126(1)	25(1)
C(16)	8496(2)	6341(2)	7852(1)	28(1)
C(17)	9427(2)	7761(2)	8360(1)	27(1)
C(18)	9877(2)	9797(2)	8142(1)	28(1)
C(19)	9389(2)	10429(2)	7424(1)	26(1)
C(20)	9349(2)	5349(3)	9347(1)	41(1)

Table 20- Bond lengths [Å] and angles [°] for trifluoro-aryl-β-lactam 280b

Bond	Length (Å)	Bond	Length (Å)
F(1)-C(11)	1.331(6)	F(2)-C(11)	1.333(6)
F(3)-C(11)	1.325(5)	F(1A)-C(11)	1.300(6)
F(2A)-C(11)	1.296(6)	F(3A)-C(11)	1.315(6)
O(1)-C(1)	1.2157(15)	O(2)-C(17)	1.3667(14)
O(2)-C(20)	1.4252(18)	N(1)-C(1)	1.3697(15)
N(1)-C(12)	1.4698(15)	N(1)-C(3)	1.4869(14)
C(1)-C(2)	1.5327(16)	C(2)-C(10)	1.5334(18)
C(2)-C(3)	1.5517(16)	C(2)-H(2)	1.0000
C(3)-C(4)	1.5027(16)	C(3)-H(3)	1.0000
C(4)-C(5)	1.3918(17)	C(4)-C(9)	1.3946(17)
C(5)-C(6)	1.3914(16)	C(5)-H(5)	0.9500
C(6)-C(7)	1.395(2)	C(6)-C(11)	1.4956(19)
C(7)-C(8)	1.390(2)	C(7)-H(7)	0.9500
C(8)-C(9)	1.3946(17)	C(8)-H(8)	0.9500
C(9)-C(10)	1.5140(17)	C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900	C(12)-C(14)	1.5159(16)
C(12)-C(13)	1.5223(16)	C(12)-H(12)	1.0000
C(13)-H(13A)	0.9800	C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800	C(14)-C(15)	1.3830(17)
C(14)-C(19)	1.4034(16)	C(15)-C(16)	1.4006(17)
C(15)-H(15)	0.9500	C(16)-C(17)	1.3893(17)
C(16)-H(16)	0.9500	C(17)-C(18)	1.3917(18)
C(18)-C(19)	1.3823(17)	C(18)-H(18)	0.9500
C(19)-H(19)	0.9500	C(20)-H(20A)	0.9800
C(20)-H(20B)	0.9800	C(20)-H(20C)	0.9800
C(17)-O(2)-C(20)	117.36(11)	C(1)-N(1)-C(12)	133.82(9)
C(1)-N(1)-C(3)	93.91(9)	C(12)-N(1)-C(3)	126.45(9)
O(1)-C(1)-N(1)	132.64(12)	O(1)-C(1)-C(2)	134.37(11)
N(1)-C(1)-C(2)	92.98(9)	C(1)-C(2)-C(10)	119.54(10)

Table 20 continued

Bond	Length (Å)	Bond	Length (Å)
C(1)-C(2)-C(3)	85.27(8)	C(10)-C(2)-C(3)	108.19(9)
C(1)-C(2)-H(2)	113.5	C(10)-C(2)-H(2)	113.5
C(3)-C(2)-H(2)	113.5	N(1)-C(3)-C(4)	116.35(9)
N(1)-C(3)-C(2)	87.83(8)	C(4)-C(3)-C(2)	104.74(9)
N(1)-C(3)-H(3)	114.8	C(4)-C(3)-H(3)	114.8
C(2)-C(3)-H(3)	114.8	C(5)-C(4)-C(9)	120.83(11)
C(5)-C(4)-C(3)	128.26(11)	C(9)-C(4)-C(3)	110.87(10)
C(6)-C(5)-C(4)	118.46(11)	C(6)-C(5)-H(5)	120.8
C(4)-C(5)-H(5)	120.8	C(5)-C(6)-C(7)	121.10(12)
C(5)-C(6)-C(11)	119.13(12)	C(7)-C(6)-C(11)	119.77(12)
C(8)-C(7)-C(6)	120.12(12)	C(8)-C(7)-H(7)	119.9
C(6)-C(7)-H(7)	119.9	C(7)-C(8)-C(9)	119.17(12)
C(7)-C(8)-H(8)	120.4	C(9)-C(8)-H(8)	120.4
C(4)-C(9)-C(8)	120.31(12)	C(4)-C(9)-C(10)	112.07(11)
C(8)-C(9)-C(10)	127.60(12)	C(9)-C(10)-C(2)	104.08(10)
C(9)-C(10)-H(10A)	110.9	C(2)-C(10)-H(10A)	110.9
C(9)-C(10)-H(10B)	110.9	C(2)-C(10)-H(10B)	110.9
H(10A)-C(10)-H(10B)	109.0	F(2A)-C(11)-F(1A)	108.2(6)
F(2A)-C(11)-F(3A)	107.0(6)	F(1A)-C(11)-F(3A)	105.7(5)
F(2A)-C(11)-F(3)	95.7(6)	F(1A)-C(11)-F(3)	115.3(6)
F(3A)-C(11)-F(3)	12.6(7)	F(2A)-C(11)-F(1)	115.0(6)
F(1A)-C(11)-F(1)	10.9(8)	F(3A)-C(11)-F(1)	95.2(6)
F(3)-C(11)-F(1)	105.4(5)	F(2A)-C(11)-F(2)	12.6(8)
F(1A)-C(11)-F(2)	96.1(6)	F(3A)-C(11)-F(2)	115.1(6)
F(3)-C(11)-F(2)	104.9(5)	F(1)-C(11)-F(2)	103.7(5)
F(2A)-C(11)-C(6)	111.4(4)	F(1A)-C(11)-C(6)	111.9(5)
F(3A)-C(11)-C(6)	112.4(5)	F(3)-C(11)-C(6)	113.2(4)
F(1)-C(11)-C(6)	114.5(4)	F(2)-C(11)-C(6)	114.1(4)
N(1)-C(12)-C(14)	109.55(9)	N(1)-C(12)-C(13)	110.74(10)
C(14)-C(12)-C(13)	113.01(9)	N(1)-C(12)-H(12)	107.8

Table 20 continued

Bond	Length (Å)	Bond	Length (Å)
C(14)-C(12)-H(12)	107.8	C(13)-C(12)-H(12)	107.8
C(12)-C(13)-H(13A)	109.5	C(12)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5	C(12)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5	H(13B)-C(13)-H(13C)	109.5
C(15)-C(14)-C(19)	117.91(11)	C(15)-C(14)-C(12)	121.01(10)
C(19)-C(14)-C(12)	121.06(11)	C(14)-C(15)-C(16)	122.20(11)
C(14)-C(15)-H(15)	118.9	C(16)-C(15)-H(15)	118.9
C(17)-C(16)-C(15)	118.72(12)	C(17)-C(16)-H(16)	120.6
C(15)-C(16)-H(16)	120.6	O(2)-C(17)-C(16)	124.60(12)
O(2)-C(17)-C(18)	115.46(11)	C(16)-C(17)-C(18)	119.93(11)
C(19)-C(18)-C(17)	120.53(11)	C(19)-C(18)-H(18)	119.7
C(17)-C(18)-H(18)	119.7	C(18)-C(19)-C(14)	120.70(12)
C(18)-C(19)-H(19)	119.7	C(14)-C(19)-H(19)	119.7
O(2)-C(20)-H(20A)	109.5	O(2)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5	O(2)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5	H(20B)-C(20)-H(20C)	109.5

Table 21- Anisotropic displacement parameters ($Å^2$ x 10^3) for trifluoro-aryl-β-lactam 280b. The anisotropic displacement factor exponent takes the form: -2 gpi^2 [h^2 a^{*2} U11 + ... + 2 h k a* b* U

Atom	U11	U22	U33	U23	U13	U12
F(1)	58(3)	59(2)	46(2)	15(2)	-16(2)	-29(2)
F(2)	158(5)	35(2)	27(2)	4(2)	25(3)	13(3)
F(3)	38(1)	116(5)	32(2)	16(2)	17(1)	0(2)
F(1A)	43(2)	149(6)	69(4)	53(4)	-12(2)	-14(3)
F(2A)	148(5)	47(3)	38(3)	8(2)	-7(2)	-46(3)
F(3A)	123(5)	87(3)	36(2)	-6(2)	39(3)	23(3)
O(1)	40(1)	38(1)	44(1)	16(1)	15(1)	-1(1)
O(2)	42(1)	37(1)	26(1)	4(1)	-2(1)	-3(1)
N(1)	22(1)	24(1)	26(1)	2(1)	6(1)	-1(1)
C(1)	27(1)	24(1)	28(1)	2(1)	4(1)	-2(1)
C(2)	24(1)	23(1)	29(1)	2(1)	3(1)	-1(1)
C(3)	20(1)	19(1)	26(1)	0(1)	5(1)	-1(1)
C(4)	20(1)	21(1)	29(1)	-3(1)	7(1)	-3(1)
C(5)	23(1)	24(1)	28(1)	-2(1)	7(1)	-3(1)
C(6)	28(1)	32(1)	28(1)	-5(1)	10(1)	-7(1)
C(7)	33(1)	32(1)	37(1)	-12(1)	14(1)	-8(1)
C(8)	29(1)	23(1)	45(1)	-8(1)	13(1)	-2(1)
C(9)	22(1)	22(1)	36(1)	-3(1)	8(1)	-3(1)
C(10)	29(1)	21(1)	38(1)	1(1)	5(1)	2(1)
C(11)	40(1)	41(1)	26(1)	-4(1)	8(1)	-9(1)
C(12)	21(1)	25(1)	26(1)	-2(1)	5(1)	0(1)
C(13)	26(1)	42(1)	33(1)	1(1)	11(1)	0(1)
C(14)	17(1)	26(1)	27(1)	-2(1)	3(1)	2(1)
C(15)	23(1)	23(1)	29(1)	-5(1)	3(1)	-1(1)
C(16)	27(1)	23(1)	33(1)	0(1)	4(1)	-1(1)
C(17)	24(1)	30(1)	25(1)	0(1)	2(1)	2(1)
C(18)	25(1)	29(1)	28(1)	-5(1)	1(1)	-4(1)
C(19)	25(1)	22(1)	32(1)	-3(1)	5(1)	-3(1)
C(20)	50(1)	40(1)	31(1)	8(1)	6(1)	-1(1)

Table 22- Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for trifluoro-aryl-β-lactam 280b.

Atom	x	y	z	U(eq)
H(2)	2777	12607	5422	30
H(3)	3857	9774	6225	26
H(5)	5355	9536	7784	30
H(7)	3626	14745	8807	40
H(8)	2863	16503	7685	38
H(10A)	3924	16181	6229	35
H(10B)	1837	15185	6162	35
H(12)	7243	8484	5838	29
H(13A)	10053	11747	6028	49
H(13B)	8971	10960	5255	49
H(13C)	10370	9375	5753	49
H(15)	7413	6027	6776	30
H(16)	8182	4947	7995	33
H(18)	10525	10759	8489	33
H(19)	9702	11824	7283	31
H(20A)	9897	4154	9112	61
H(20B)	7971	5274	9237	61
H(20C)	9746	5269	9876	61

Table 23- Dihedral angles for trifluoro-aryl-β-lactam 280b.

Atom1 - Atom2 - Atom3 - Atom4	Dihedral (°)
C(12) - N(1) - C(1) - O(1)	-25.3(2)
C(3) - N(1) - C(1) - O(1)	-178.26(16)
C(12) - N(1) - C(1) - C(2)	154.04(12)
C(3) - N(1) - C(1) - C(2)	1.06(9)
O(1) - C(1) - C(2) - C(10)	-73.46(19)
N(1) - C(1) - C(2) - C(10)	107.24(11)
O(1) - C(1) - C(2) - C(3)	178.28(16)
N(1) - C(1) - C(2) - C(3)	-1.02(9)
C(1) - N(1) - C(3) - C(4)	-106.43(11)
C(12) - N(1) - C(3) - C(4)	97.62(13)
C(1) - N(1) - C(3) - C(2)	-1.04(9)
C(12) - N(1) - C(3) - C(2)	-157.00(11)
C(1) - C(2) - C(3) - N(1)	0.93(8)
C(10) - C(2) - C(3) - N(1)	-118.64(10)
C(1) - C(2) - C(3) - C(4)	117.64(9)
C(10) - C(2) - C(3) - C(4)	-1.94(12)
N(1) - C(3) - C(4) - C(5)	-85.76(14)
C(2) - C(3) - C(4) - C(5)	179.27(11)
N(1) - C(3) - C(4) - C(9)	96.43(11)
C(2) - C(3) - C(4) - C(9)	1.47(12)
C(9) - C(4) - C(5) - C(6)	0.38(17)
C(3) - C(4) - C(5) - C(6)	-177.23(11)
C(4) - C(5) - C(6) - C(7)	-0.62(17)
C(4) - C(5) - C(6) - C(11)	179.19(10)
C(5) - C(6) - C(7) - C(8)	0.46(18)
C(11) - C(6) - C(7) - C(8)	-179.35(12)
C(6) - C(7) - C(8) - C(9)	-0.04(18)
C(5) - C(4) - C(9) - C(8)	0.03(17)
C(3) - C(4) - C(9) - C(8)	178.02(10)
C(5) - C(4) - C(9) - C(10)	-178.42(11)

Table 23 continued

Atom1 - Atom2 - Atom3 - Atom4	Dihedral (°)
C(3) - C(4) - C(9) - C(10)	-0.43(13)
C(7) - C(8) - C(9) - C(4)	-0.20(18)
C(7) - C(8) - C(9) - C(10)	177.99(12)
C(4) - C(9) - C(10) - C(2)	-0.81(13)
C(8) - C(9) - C(10) - C(2)	-179.13(11)
C(1) - C(2) - C(10) - C(9)	-93.27(12)
C(3) - C(2) - C(10) - C(9)	1.69(12)
C(5) - C(6) - C(11) - F(2A)	-32.1(5)
C(7) - C(6) - C(11) - F(2A)	147.8(5)
C(5) - C(6) - C(11) - F(1A)	89.1(5)
C(7) - C(6) - C(11) - F(1A)	-91.1(5)
C(5) - C(6) - C(11) - F(3A)	-152.2(4)
C(7) - C(6) - C(11) - F(3A)	27.6(4)
C(5) - C(6) - C(11) - F(3)	-138.6(4)
C(7) - C(6) - C(11) - F(3)	41.2(4)
C(5) - C(6) - C(11) - F(1)	100.6(4)
C(7) - C(6) - C(11) - F(1)	-79.6(4)
C(5) - C(6) - C(11) - F(2)	-18.7(5)
C(7) - C(6) - C(11) - F(2)	161.1(5)
C(1) - N(1) - C(12) - C(14)	154.93(12)
C(3) - N(1) - C(12) - C(14)	-59.36(14)
C(1) - N(1) - C(12) - C(13)	29.62(17)
C(3) - N(1) - C(12) - C(13)	175.32(10)
N(1) - C(12) - C(14) - C(15)	111.89(12)
C(13) - C(12) - C(14) - C(15)	-124.12(12)
N(1) - C(12) - C(14) - C(19)	-66.36(13)
C(13) - C(12) - C(14) - C(19)	57.63(15)
C(19) - C(14) - C(15) - C(16)	1.61(17)
C(12) - C(14) - C(15) - C(16)	-176.69(10)
C(14) - C(15) - C(16) - C(17)	-1.13(17)

Table 23 continued

Atom1 - Atom2 - Atom3 - Atom4	Dihedral (°)
C(20) - O(2) - C(17) - C(16)	-8.16(18)
C(15) - C(16) - C(17) - O(2)	-179.30(11)
C(15) - C(16) - C(17) - C(18)	-0.03(17)
O(2) - C(17) - C(18) - C(19)	179.98(11)
C(16) - C(17) - C(18) - C(19)	0.64(18)
C(17) - C(18) - C(19) - C(14)	-0.13(18)
C(15) - C(14) - C(19) - C(18)	-0.97(17)
C(12) - C(14) - C(19) - C(18)	177.33(10)

5.5 X-ray Crystal Structure Data for *Gem*-Dimethyl β-lactam 373

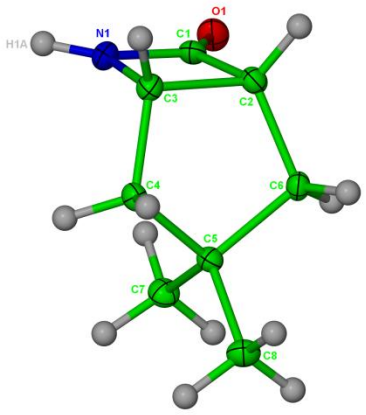


Figure 38- X-ray crystal structure of *gem*-dimethyl β-lactam 373 with ellipsoids drawn at the 50% probability level.

Table 24- Crystal data and structure refinement for *gem*-dimethyl β-lactam 373

Identification code	k11sdb1
Empirical formula	C8 H13 N O
Formula weight	139.19
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P212121
Unit cell dimensions	a = 5.7340(1)Å α = 90^o
	b = 6.4170(1)Å β = 90^o
	c = 21.4780(5)Å γ = 90^o
Volume	790.28(3) Å^3
Z	4
Density (calculated)	1.170 Mg/m^3
Absorption coefficient	0.077 mm^{-1}
F(000)	304
Crystal size	0.50 x 0.40 x 0.40 mm
Theta range for data collection	3.70 to 27.40 ^{o}.
Index ranges	-7<=h<=7; -8<=k<=8; -27<=l<=26
Reflections collected	11687
Independent reflections	1784 [R(int) = 0.0527]
Reflections observed (>2σ)	1425
Data Completeness	0.995
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.970 and 0.898
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1784 / 0 / 95
Goodness-of-fit on F^2	1.044
Final R indices [I>2σ(I)]	R1 = 0.0400 wR2 = 0.0949
R indices (all data)	R1 = 0.0581 wR2 = 0.1042
Absolute structure parameter	1.5(19)
Largest diff. peak and hole	0.196 and -0.248 eÅ^{-3}

Notes: Intermolecular hydrogen-bonding present in the gross structure.

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
N1-H1A	0.880	2.021	166.89	2.885	O1 [-x+2, y+1/2, -z+1/2]

Table 25- Atomic coordinates (x 10^4) and equivalent isotropicdisplacement parameters (Å^2 x 10^3) for *gem*-dimethyl β-lactam 373. U(eq) is definedas one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
O(1)	9553(2)	9615(2)	1820(1)	41(1)
N(1)	7665(2)	12529(2)	2251(1)	34(1)
C(1)	7997(3)	10913(2)	1864(1)	31(1)
C(2)	5740(3)	11349(2)	1503(1)	30(1)
C(3)	5505(3)	13254(2)	1949(1)	31(1)
C(4)	5722(3)	15198(2)	1550(1)	29(1)
C(5)	6838(3)	14522(2)	924(1)	27(1)
C(6)	6025(3)	12242(3)	849(1)	29(1)
C(7)	9514(3)	14667(3)	945(1)	35(1)
C(8)	5969(3)	15884(3)	390(1)	38(1)

Table 26- Bond lengths and angles for *gem*-dimethyl β-lactam 373

Bond	Length (Å)	Bond	Length (Å)
O(1)-C(1)	1.224(2)	N(1)-C(1)	1.343(2)
N(1)-C(3)	1.473(2)	N(1)-H(1A)	0.8800
C(1)-C(2)	1.534(2)	C(2)-C(6)	1.526(2)
C(2)-C(3)	1.559(2)	C(2)-H(2)	1.0000
C(3)-C(4)	1.519(2)	C(3)-H(3)	1.0000
C(4)-C(5)	1.550(2)	C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900	C(5)-C(8)	1.526(2)
C(5)-C(7)	1.538(2)	C(5)-C(6)	1.544(2)
C(6)-H(6A)	0.9900	C(6)-H(6B)	0.9900
C(7)-H(7A)	0.9800	C(7)-H(7B)	0.9800
C(7)-H(7C)	0.9800	C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800	C(8)-H(8C)	0.9800
C(1)-N(1)-C(3)	95.23(12)	C(1)-N(1)-H(1A)	132.4
C(3)-N(1)-H(1A)	132.4	O(1)-C(1)-N(1)	132.60(15)
O(1)-C(1)-C(2)	134.40(14)	N(1)-C(1)-C(2)	92.99(13)
C(6)-C(2)-C(1)	116.32(13)	C(6)-C(2)-C(3)	106.33(12)
C(1)-C(2)-C(3)	84.57(11)	C(6)-C(2)-H(2)	115.2
C(1)-C(2)-H(2)	115.2	C(3)-C(2)-H(2)	115.2
N(1)-C(3)-C(4)	116.01(13)	N(1)-C(3)-C(2)	87.14(11)
C(4)-C(3)-C(2)	106.82(12)	N(1)-C(3)-H(3)	114.5
C(4)-C(3)-H(3)	114.5	C(2)-C(3)-H(3)	114.5
C(3)-C(4)-C(5)	107.06(12)	C(3)-C(4)-H(4A)	110.3
C(5)-C(4)-H(4A)	110.3	C(3)-C(4)-H(4B)	110.3
C(5)-C(4)-H(4B)	110.3	H(4A)-C(4)-H(4B)	108.6
C(8)-C(5)-C(7)	108.23(14)	C(8)-C(5)-C(6)	111.42(13)
C(7)-C(5)-C(6)	111.19(14)	C(8)-C(5)-C(4)	110.92(13)
C(7)-C(5)-C(4)	111.68(13)	C(6)-C(5)-C(4)	103.40(12)
C(2)-C(6)-C(5)	106.93(12)	C(2)-C(6)-H(6A)	110.3
C(5)-C(6)-H(6A)	110.3	C(2)-C(6)-H(6B)	110.3

Table 26 continued

Bond	Length (Å)	Bond	Length (Å)
C(5)-C(6)-H(6B)	110.3	H(6A)-C(6)-H(6B)	108.6
C(5)-C(7)-H(7A)	109.5	C(5)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5	C(5)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5	H(7B)-C(7)-H(7C)	109.5
C(5)-C(8)-H(8A)	109.5	C(5)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5	C(5)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5	H(8B)-C(8)-H(8C)	109.5

Table 27 - Anisotropic displacement parameters ($Å^2$ x 10^3) for *gem*-dimethyl β-lactam 373. The anisotropic displacement factor exponent takes the form: -2 gpi^2 [h^2 a^{*2} U11 + ... + 2 h k a* b* U

Atom	U11	U22	U33	U23	U13	U12
O(1)	49(1)	31(1)	42(1)	4(1)	-12(1)	6(1)
N(1)	42(1)	35(1)	26(1)	0(1)	-6(1)	-4(1)
C(1)	41(1)	25(1)	28(1)	6(1)	-4(1)	-5(1)
C(2)	32(1)	26(1)	32(1)	1(1)	-3(1)	-4(1)
C(3)	33(1)	32(1)	27(1)	-1(1)	1(1)	-2(1)
C(4)	30(1)	25(1)	31(1)	-3(1)	0(1)	-1(1)
C(5)	27(1)	26(1)	28(1)	1(1)	0(1)	-3(1)
C(6)	33(1)	28(1)	26(1)	-4(1)	-5(1)	0(1)
C(7)	30(1)	37(1)	37(1)	1(1)	4(1)	-3(1)
C(8)	42(1)	35(1)	36(1)	8(1)	0(1)	1(1)

Table 28- Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for *gem*-dimethyl β-lactam 373

Atom	x	y	z	U(eq)
H(1A)	8461	12994	2572	57(6)
H(2)	4499	10265	1547	36
H(3)	4095	13222	2223	37
H(4A)	6717	16245	1760	34
H(4B)	4166	15820	1477	34
H(6A)	4524	12188	621	35
H(6B)	7197	11431	612	35
H(7A)	9978	16105	1036	52
H(7B)	10158	14246	542	52
H(7C)	10112	13743	1272	52
H(8A)	6651	15396	-2	56
H(8B)	6435	17333	463	56
H(8C)	4266	15798	365	56

Table 29 - Dihedral angles for *gem*-dimethyl β-lactam 373

Atom1 - Atom2 - Atom3 - Atom4	Dihedral (°)
C(3) - N(1) - C(1) - O(1)	176.83(17)
C(3) - N(1) - C(1) - C(2)	-2.25(12)
O(1) - C(1) - C(2) - C(6)	-71.4(2)
N(1) - C(1) - C(2) - C(6)	107.67(14)
O(1) - C(1) - C(2) - C(3)	-176.93(18)
N(1) - C(1) - C(2) - C(3)	2.13(11)
C(1) - N(1) - C(3) - C(4)	-105.12(15)
C(1) - N(1) - C(3) - C(2)	2.21(12)
C(6) - C(2) - C(3) - N(1)	-117.80(13)
C(1) - C(2) - C(3) - N(1)	-1.94(10)
C(6) - C(2) - C(3) - C(4)	-1.46(16)
C(1) - C(2) - C(3) - C(4)	114.40(13)
N(1) - C(3) - C(4) - C(5)	77.69(16)
C(2) - C(3) - C(4) - C(5)	-17.45(16)
C(3) - C(4) - C(5) - C(8)	148.77(14)
C(3) - C(4) - C(5) - C(7)	-90.41(16)
C(3) - C(4) - C(5) - C(6)	29.23(15)
C(1) - C(2) - C(6) - C(5)	-72.09(17)
C(3) - C(2) - C(6) - C(5)	19.91(16)
C(8) - C(5) - C(6) - C(2)	-149.34(14)
C(7) - C(5) - C(6) - C(2)	89.83(16)
C(4) - C(5) - C(6) - C(2)	-30.15(16)

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